Regulation and Adoption Dynamics of Pharmaceutical Technologies: Evidence from the OECD, 1999-2008

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DECLARATION

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ABSTRACT

This thesis examines adoption of pharmaceutical technologies across the major OECD markets during 1999-2008, a period that has witnessed substantial R&D productivity shortfalls and increasing supply-side pressure on pharmaceutical pricing. The advent of the financial crisis in 2008 has resulted in even more stringent pricing and reimbursement (P&R) regulations to contain costs and ensure value for money in pricing decisions. The central theoretical question addressed, therefore, is how price regulation affects cross-national adoption dynamics of pharmaceutical technologies. I address the impact of regulation on: i) innovative technologies, i.e. patent-protected new molecules that are central to dynamic efficiency, and ii) imitative generic technologies, i.e. lower-priced bioequivalent products that are central to static efficiency. The research in this thesis was motivated by the lack of theoretical framework or empirical evidence on the dynamics of international technology adoption in general and marked delay patterns in the adoption of pharmaceutical technologies observed in practice. It is important to understand the regulatory factors driving these delays given the profound implications of such delays on consumer and producer welfare as well as healthcare provider/payer budgets. The main hypothesis in this thesis is that price controls negatively affect adoption speed for new molecules and generics in markets that employ price controls as these controls reduce incentives to entry and result in knock-on effects in foreign markets because of linkages such as reference pricing and parallel trade. The empirical strategy adopts difference-in-difference and survival analysis using IMS data from 20 markets and controls for heterogeneity in firm and molecule characteristics.Overall findings indicate that adoption of pharmaceutical technologies is slower in price-controlled markets and that firms adapt their launch strategies to changes in pharmaceutical regulations. Expected market size is a highly significant driver of generic launch hazard, which highlights the importance of demand-side policies to promote generic use.

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ABBREVIATIONS

AIC	Akaike's Information Criteria
AIFA	Agenzia Italiana del Farmaco; Italian Medicines Agency
ANDA	Abridged New Drug Application
ATC	Anatomic Therapeutic Classification
BIC	Bayesian Information Criteria
CLOGLOG	Complementary Log Log
CPI	Corruption Perception Index
DG	Directorate General
EC	European Commission
EEA-EFTA	European Economic Area-European Free Trade Association
EEC	European Economic Community
EMEA/EMA	European Medicines Agency
EPC	European Patent Convention
EU	European Union
EU5	France, Germany, Italy, Spain, UK
FRA	France
FDA	Food and Drug Administration
FOC	First Order Conditions
G7	Canada, France, Germany, Italy, Japan, UK, US
GDP	Gross Domestic Product
GER	Germany
HAS	Haute Autorité de santé; French National Authority for Health
HMO	Health Maintenance Organization
HTA	Heath Technology Assessment
ICH	International Conference on Harmonisation
IHH	Herfindahl-Hirschman Index
IMS	Intercontinental Medical Statistics
IP	Intellectual Property
IPS	Intellectual Property Rights
IQWiG	German Institute for Quality and Efficiency in Health Care
ITA	Italy
JAP	Japan
MA	Marketing Authorization
NCE	New Chemical Entity
NDA	New Drug Application
NICE	National Institute of Clinical Excellence
OECD	Organisation for Economic Co-operation and Development
OLS	Ordinary Least Squares
OTC	Over-the-Counter
P&R	Pricing and Reimbursement
PH	Proportional Hazard

PPRS	Pharmaceutical Price Regulation Scheme
Q	Quarter
R&D	Research and Development
RP	Reference Pricing
RPS	Reference Pricing System
SPA	Spain
SPC	Supplementary Protection Certificate
SU	Standard Unit
TRIPS	Trade Related Aspects of Intellectual Property Rights
USD	United States Dollars
VAT	Value Added Tax
VIF	Variance Inflation Factor

CHAPTER 1

1 INTRODUCTION

The pharmaceutical industry is an industry of high political and economical relevance. It has always drawn the attention of economists in the field of industrial organization due to its rich set of features that include patent protection, high research and development (R&D) investments, intense product promotion and heavy regulation. The pharmaceutical industry is one of the most heavily regulated industries because of safety and health concerns of products and relatively high profits the industry has enjoyed historically. In 2005, pharmaceutical firms in the Fortune 500 averaged a 10.3% return on assets, whereas the median for all US industries was 4.7%[1].

Pharmaceutical policies in different countries rely on pricing and reimbursement (P&R) schemes to ensure access to medicines according to need; control pharmaceutical and total healthcare expenditure; and ensure efficiency (cost-effectiveness) of resources allocated to pharmaceutical care. The advent of the recent financial crisis and the need for fiscal austerity to tackle budget deficits has increased the reliance on more stringent pharmaceutical P&R controls. There is a growing emphasis on value based pricing (VBP) in major markets, especially in the UK where the government has recently proposed to replace the current Pharmaceutical Price Regulation Scheme (PPRS). Although this seems now to be on hold, any new VBP system could have significant global knock-on effects in countries that reference the UK, which make up approximately 25% of the global market according to the Office of Fair Trading (O.F.T 2007; Hirschler 2010).

In light of the increasing pressure on drug prices, it is important from a policy perspective to analyze the potential effects of price controls on the adoption of pharmaceutical products and patient access to necessary treatments. The evidence regarding the impact of regulation on the launch timing of pharmaceutical technologies across different markets is scanty. The aim of this thesis is to improve our understanding of the effects of regulation on the speed of adoption of new pharmaceutical products and inform future pharmaceutical pricing policies. Given the complementary nature of the branded and generic sector from a social welfare

[1] Profit measures, however, may be overstated for R&D intensive industries as R&D expenditures are not treated as a capitalised investment (CBO 2006).

perspective, the thesis aims to investigate the impact of price controls on entry of both innovative products and generic competition in the OECD during 1999-2008.

This chapter is organized as follows: Section 1.1 provides an introduction into the concepts of innovation, competition and static-dynamic efficiency trade-off in the pharmaceutical industry that are often referred to in the thesis; Section 1.2 defines market barriers to entry in the pharmaceutical sector and discusses the rationale for regulation in the pharmaceutical sector; Section 1.3 provides an overview of different P&R regulations in the main OECD markets and summarizes main findings on the impact of pharmaceutical regulation; and finally Section 1.5 outlines the organization of the thesis and states the main research questions and hypotheses in individual chapters.

1.1 Innovation, Competition and Efficiency in the Pharmaceutical Industry

An extensive body of research has been carried out on the economics of the pharmaceutical industry (Scherer 2000; Schweitzer and Comanor 2007). This section will focus on a subset of key concepts such as innovation and competition that define the analytical framework in this thesis, and highlight the inherent trade-off between static and dynamic efficiency central to policymaking decisions in the pharmaceutical industry.

Innovation is broadly defined as a technological progress that leads to an entirely new product or an increase in the therapeutic value of an existing product (product innovation), or a change in the cost of production or service (process innovation). Product innovation entails new qualities or a combination of existing qualities. It usually results in increased production costs compared to existing alternatives. Pharmaceutical product innovation can be based on new active substances, new indications for existing products or new ways of administering the same product. Zweifel and Breyer (2009) also define organizational innovation that involves cost reductions in the production of a good or service through a reorganization of production processes and/or restructuring of entire firms (e.g. separation of internal medicine and geriatric care in hospitals and creation of Health Maintenance Organizations) (Zweifel, Breyer et al. 2009). Innovation in this thesis is defined as the development of new molecules (new active ingredients) in a given therapeutic area. This definition ignores new indications or forms for a given molecule and process innovations are ignored.

Innovation is central to the competitiveness of the pharmaceutical industry. New goods are drivers of economic progress and sustainable growth (Bresnahan and Gordon 1997). According to empirical evidence pharmaceutical innovation in the form of new drug approvals has contributed significantly to longevity increase since 1960's (Lichtenberg 2003b; Lichtenberg 2004; Lichtenberg 2005). Pharmaceuticals are considered as one of the most cost effective forms of healthcare (Grootendorst, Piérard et al. 2009). Although the majority of the pharmaceutical innovation comes in gradual or marginal improvements over existing products (Lexchin 2004)[2], patients using newer drugs have lower mortality rates controlling for age, sex, religion, diagnosis and utilization of medical services (Jung and Lichtenberg 2006; Lichtenberg, Grootendorst et al. 2009; Lichtenberg 2010).

Pharmaceutical products have several quality dimensions, including efficacy, safety and the convenience of the product. Only new molecules that show significant innovative benefits over existing treatments in meeting an unmet clinical need can get premium prices. Adoption of pharmaceutical innovation therefore is essential to address unmet medical needs and improve public health outcomes and quality of life. Pharmaceutical innovation is extremely expensive to develop. As one of the most R&D intensive industries, for each molecule an investment of $800 million is required, depending on the therapy or the developing firm this cost could go up to $2,000 million (DiMasi 2002; DiMasi, Hansen et al. 2003; Adams and Brantner 2006).

Economically efficient R&D investment requires projects with positive net present value (NPV) or projects that generate internal rate of return higher than the cost of capital. Minimum product prices required to make R&D projects economically attractive could be significantly higher than marginal costs of production. Much of the R&D cost is incurred to discover new molecules and test their efficacy in clinical trials. Imitators could free-ride on a new discovery and clinical trial information by investing only in process engineering. This would allow the introduction of the same product at a much lower price and destroy incentives for innovation on the incumbent's side. Patent protection and market exclusivity are therefore significant components of profit earning expectations and dynamic efficiency, i.e. rate of introduction of new products and production processes (Cabral 2000). On the other hand, monopoly power granted by

[2] Based on an assessments of the value of new drugs from Canada, France and the USA, Lexchin (2004) claims that at best one third of new drugs offer some additional clinical benefit and perhaps as few as 3% are major therapeutic advances.

patents allows above marginal cost pricing and reduces static efficiency. Therefore, competition policy defends market competition to increase overall welfare.

Competition stimulates firms to invest in future innovation and improve competitiveness with respect to the rivals. A monopolist will be dynamically less efficient compared to firms operating in a competitive environment. This economic trade-off between static efficiency and dynamic efficiency is inherent in R&D-based industries including the pharmaceutical industry itself. That said, the relationship between competition and innovation is not monotonically increasing. Too strong competition reduces the appropriability of investments and the incentives to innovate. An environment with some competition but high enough market power to allow appropriability of innovative activities is the most conducive to R&D.

1.1.1 Competitive Structure: Branded vs. Generic Competition

The level of competition is often key to firm and industry behaviour as it drives prices closer to marginal costs and provides incentives for innovation. Although the industry is dominated by the major pharmaceutical companies (big pharma), it exhibits high levels of fluidity with frequent entry and departure of firms. However, the worldwide market is witnessing decreasing competitiveness due to mergers and acquisitions (M&A) and consolidation of top selling drugs sales among fewer firms (Schweitzer and Comanor 2007). The degree of market concentration is much higher within a specific therapeutic class comprised of products that compete with one another. Therapeutic classes are defined based on the Anatomical Therapeutic Classification System (ATC) that groups drug products by anatomical site of action, chemical properties, pharmacological and therapeutic properties. Throughout this thesis competition is defined at the anatomical/therapeutic/pharmacological and chemical subgroup level (ATC4) (see Appendix A.1 for the description of the ATC System).

Pharmaceutical markets are subject to two types of competition: pre-patent (branded) and post-patent (generic) competition. The prices of both brand-name and generics are often lower when a higher number of drugs exist. Competition between patent-protected molecules (branded competition) in a given therapeutic category depends on the relative qualities of the new molecule and incumbent molecules. The degree of innovation is a key driver of new molecule prices and thus dynamic efficiency. The degree of competition in the branded sector is not perfect. Single-sourced drugs can raise prices

above marginal costs due to unavailability of substitutes. Promotion efforts may reinforce habits of physicians and result in price insensitivity due to brand loyalty.

Government policies are increasingly promoting the use of generic drugs worldwide. Generic drugs are bioequivalent to the brand name reference drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use. Generics, therefore, are typically classified as commodity products that compete based on price. Generics offer significant discounts compared to branded drugs. Estimated annual savings due to generic drug use are about $8 to $10 bn a year at US retail pharmacies, €0.9 bn in Germany, €0.5 bn in France and €0.4 bn in the UK (Simoens and de Coster 2006; FDA 2010).

Stronger generic competition increases the importance of the exclusivity period because of erosion in price and sales volume of the originator product after patent expiry (which increases static efficiency). Firms can target incremental innovation to increase the period of market exclusivity. However, bringing completely new products to the market is absolutely necessary to maintain a competitive product portfolio. Therapeutically important products can easily substitute others in the market. Therefore, generic competition drives R&D oriented firms to invest into new products that will gain market acceptance quickly and generate sufficient returns.

1.1.2 Static vs. Dynamic Efficiency Trade-off

Static efficiency, the maximization of social welfare at a particular point in time, requires that the market structure is highly competitive and no firm holds market power. For a given production technology, when prices are above marginal costs the increase in producer surplus does not compensate for the reduction in consumer surplus (allocative inefficiency). The higher the size of the market and the lower price elasticity of demand, the higher is the efficiency loss due to monopoly pricing (Motta 2004). High market power might also result in dynamic inefficiencies. A monopolist sheltered from competition may not have sufficient incentives to adopt the most efficient technologies and to invest in R&D. Eliminating market power ex-post to reduce prices and increase static (allocative) efficiency, however, would eliminate ex-ante incentives for innovation and decrease dynamic efficiency.

The static versus dynamic efficiency trade-off in the pharmaceutical industry requires considering both the on-patent and off-patent sectors for a holistic analysis. The thesis,

therefore, investigates the impact of price controls on the adoption of new products both in the on-patent and off-patent sector.

Static-dynamic efficiency trade-off is becoming more severe as the cost of R&D continues to increase substantially (Charles River Associates 2004). A central question in competition policy and regulation is the optimum degree of intervention. In an ideal environment, competition would not be restricted in a way that is detrimental to society but also market power would be preserved for future innovative activities. This thesis aims to provide positive empirical evidence regarding the impact of price controls on adoption of pharmaceuticals. However, the optimal form of pharmaceutical regulation and the degree of price mark-up consistent with dynamic efficiency will not be addressed.

1.1.3 Adoption and Diffusion of Innovations

In the economics literature, technology adoption referes to the decision at the individual level to acquire a new invention or innovation whereas diffusion refers to the process through which technology spreads across a population (Hall and Khan 2003). In the pharmaceutical context, adoption is the first contact of the physician with the innovation and diffusion is the rate at which the new drug dispensed over time (Serra-Sastre and McGuire 2009). There is considerable theoretical framework and empirical evidence regarding the diffusion of new technologies (Stoneman 2002; Serra-Sastre 2008). Boradly speaking, adoption and diffusion of innovations is decomposed into two levels: the inter-firm level and the intra-firm level.

The inter-firm level, also referred as adoption, represents the first contact or use of a technology within an organization or a pool of potential adopters. This level does not explain the intensity of use once the technology is adopted. The inter-firm concept is more related to the time elapsed between technology availability and time to adoption. The intra-firm level, on the other hand, represents the intensity of use of the new technology conditional on prior adoption of the technology. It refers to the rates at which different firms produce goods using the new technology or to the diffusion of a particular innovation across the subsidiaries of a company. While inter-firm diffusion is dominant at early stages, intra-firm diffusion becomes more prominent at the later stages of the technology diffusion process.

Historically modelling of technological diffusion has relied on: i) *epidemic models* that assume an invariant population of potential adopters where non-users become users upon making a contact with prior adopters (Griliches 1957; Bain 1962); ii) *the probit or rank approach* assumes rational profit maximizing behaviour at each time point by comparing cost of acquisition and gross benefits of technology adoption (Ireland and Stoneman 1986; Stoneman and Battisti 1997; Battisti and Stoneman 2003); iii) *the stock model* that considers reduction in costs of the adopting firm and its impacts on prices of firm's products as well as output levels in the whole industry (Reinganum 1981; Schumpeter 1984; Metcalfe 1995); and iv) *the order model* which considers first mover advantages such as the ability to influence the adoption decision of other firms and gain higher returns compared to follow-on adopters (Fudenberg and Tirole 1985). Stoneman (2002) provides a comprehensive review and technical details of these models (Stoneman 2002). Most recently, technology adoption has been considered by economists in the real options framework by Dixit and Pindyck (1994). Similar to investment decicions, the adoption of new technologies is characterized by the uncertainty over future profits; sunk costs due to irreversibility and the opportunity to delay (Dixit, Pindyck et al. 1994; Stoneman 2001).

All of the above models indicate that the main drivers of diffusion are learning and information spreading, cost of new technology acquisition, performance of the new technology, price expectations, firm characteristics, risk attitudes, the extent of product differentiation, first mover advantages and the extent of new investments to be generated by realized profits. Rogers (1995) has highlighted the significant role of perceived attributes in new technology adoption. Perceived attributes of innovation theory considers the following key attributes: 1) relative advantage; 2) compatability; 3) complexity; 4) trialability; 5) observability (Rogers 1995). Relative advantage is the degree to which an innovation is perceived as being better than the idea it supersedes. It is often expressed as economic profitability, social prestige or other benefits. Compatibility is the degree to which an innovation is perceived as consistent with the existing values, past experiences, and needs of potential adopters. Complexity is the degree to which an innovation is perceived as relatively difficult to understand and to use. Trialability represents the degree to which an innovation may be experimented with on a limited basis, and finally, observability defines the degree to which the results of an innovation are visible to others.

Theories described above and the relevant empirical evidence has mainly focused on adoption and diffusion in a single geographical market. Evidence on technological adoption in a cross-country setting is extremely limited. Comin and Hobijn (2003) distinguish five main theories/hypotheses about factors that determine technological adoption in a cross-country setting: i) vintage capital theory; ii) vintage human capital; iii) general purpose technologies with complementary inventions; iv) trade; v) vested interests and political institutions (Comin and Hobijn 2003). Caselli and Coleman (2001) carry out a cross-country analysis of computer investment. Their results show that highly-skilled human capital, high investment rates, property rights and small share of the agricultural sector in GDP encourage the investment in computing equipment. The research in this thesis aims to improve the evidence base on cross-country adoption of new technologies by focusing on the pharmaceutical technologies with a particular interest on how regulation affects the differential adoption speed across OECD markets.

1.2 Economics of Regulation in the Pharmaceutical Sector

The idealized competitive market model provides a framework to define efficiency. Efficiency is measured with respect to changes in total consumer and producer surplus (social surplus or social welfare). Economic theory holds that social welfare is optimized by a free market unconstrained by government involvement in a perfectly competitive market (consistent with Pareto Efficiency, i.e. utility-maximizing behaviour of individuals and profit-maximizing behaviour of firms such that no one could be better off without making someone else worse off).

Perfect competition holds under the following key assumptions: i) consumers are perfectly informed about all goods, which are all private goods; ii) production functions rule out increasing returns to scale and technological change; iii) consumers maximize their preferences under budget constraints and producers maximize profits given their production function; iv) all agents are price takers and there are no externalities among agents; v) a competitive equilibrium exists with a set of prices that clear the market. If any of these assumptions fail, equilibrium market behaviour fails to maximize social surplus (Viscusi, Vernon et al. 2005; Weimer and Vining 2005).

The economic rationale for regulation arises from market failures. The aim of regulation is to correct market failure on the premise that introducing another market distortion (regulation) can improve efficiency (the theory of the second best). Given the extensive

failures in the pharmaceutical market (outlined in Section 1.2.1), it is unsurprising that the pharmaceutical market is among the most extensively regulated markets.

Values other than efficiency may also be considered to achieve social welfare beyond Pareto Efficiency. Regulation may also arise to correct inequity, ensure human dignity and equality in outcomes as access to essential medicines is recognized as a core part of the international right to health (Thomas 2006). Disentangling inequities from inefficiencies, however, may not be always possible. For example, inequities such as lack of access to pharmaceutical technologies, a failure of the market to address demand from a social welfare perspective, are also inefficiencies.

1.2.1 Market Failures in the Pharmaceutical Market

The pharmaceutical market demonstrates unique failures different from other industrial markets, which include but are not limited to: i) critical nature of patents to incentivize research in a high fixed-cost environment; ii) need for costly and long clinical trials to resolve the uncertainty regarding the benefits of pharmaceuticals in heterogeneous patient populations; iii) delegation of the consumption decision to an agent (the physician); iv) the dominant role of third party payment through social and/or private health insurance; v) global public good nature of pharmaceutical products; vi) positive externalities from the consumption of drugs against infectious diseases and caring externalities (altruistic preferences that make individuals care about the health of others) (Danzon and Keuffel 2007). The following section discusses market failures in the pharmaceutical industry whose correction requires government intervention.

1.2.1.1 Information Problems, Agency and Moral Hazard

The specialized knowledge involved in health care and the inefficiency for each patient (principal) to seek out all the relevant information results in the delegation of treatment choice to the physician (agent). The separation of the consumer (the patient), the decision maker (the physician) and third party payers (the government or insurance companies) due to informational asymmetries creates problems of imperfect agency and moral hazard (Bloom and Reenen 1998). Moral hazard arises when individuals engage in risk sharing (e.g., financial insulation under an insurance contract) and modify their behaviour compared to conditions under which they are fully exposed to the risk. Under such conditions Pareto-optimal risk sharing is generally precluded as the contract does

not induce proper incentives for taking correct actions (Hölmstrom 1979). Resource consumption occurs at a higher level than the optimum where marginal social benefit equals marginal social costs as insurance makes consumers price-insensitive.

Doctors may lack information on drug prices or may have limited concern for expenditure control unless they are incentivized to do so with budget constraints. This may result in inefficiencies either because prescriptions do not offer therapeutic value for money or as a result of overconsumption as the physician and/or the consumer do not face the full financial risk for pharmaceutical expenses. Similarly, ex-ante moral hazard may occur if consumers increase their risky behaviour and take fewer precautions to prevent illnesses.

1.2.1.2 Patents and Market Power

R&D in general has public good characteristics and results in positive externalities on other firms that free-ride on inventions (spillovers). Spillovers reduce the payoff of the innovator, and incentives to R&D, by creating competition in the market. If innovators cannot appropriate their R&D efforts, future investment for R&D will be less than optimal for society and will reduce dynamic efficiency. A patent provides an exclusive right (a monopoly) over the invention and restores incentives for R&D and innovation. Patents are key to the innovative activities in the pharmaceutical sector given the research intensity and cost of capital invested into pharmaceutical R&D. Given the relatively inelastic demand for pharmaceuticals (drug price elasticity is estimated to be around -0.209, which is relatively inelastic), patents allow pharmaceutical manufacturers to capture significant monopoly rents (Scherer 2000; Motta 2004; Gemmill, Costa-Font et al. 2007).

Essentially market power is given to enhance dynamic efficiency but results in a trade-off between granting firms appropriability of innovation and spread of innovative benefits to consumers. This closely ties with the static-dynamic efficiency trade-off described in Section 1.1.2, in the sense that patents improve dynamic efficiency compared to the no-patent case but inhibits competition and static efficiency. When prices are above marginal costs, the increase in producer surplus does not compensate for the reduction in consumer surplus. In addition, a loss is incurred because of the reduction in improvements made by competitors on the patented invention. This raises

issues around appropriate price and profit levels, and the optimum design or duration of patent protection (Christie and Rotstein 2008).

There is a large literature that discusses optimal length and breadth of patents (Tirole 1990). Too narrow or too short patent definition results in no incentives for innovation, whereas too broad or too long patent definition gives too much power to the incumbent and stops other firms innovating. A patent creates social costs through the inhibition of competitor innovation and static inefficiency, which increase over the duration of monopoly protection. The optimum duration is modelled by equating the marginal social benefit of a patent with the marginal social cost of the patent over time. However, determining the actual value normatively is not an easy task due to the difficulty in specifying the exact nature of marginal social costs and benefits associated with a patent (Nordhaus 1972; Wright 1983; Gilbert and Shapiro 1990; Denicolò 1996). Therefore, positive empirical evidence is essential in resolving the trade-off between static and dynamic considerations.

In many countries, the rationale for price regulation is the concern around excessive prices/profits pharmaceutical manufacturers claim in addition to the price insensitivity due to insurance coverage as described in Section 1.2.1.1. The extent of market power depends on several factors such as the concentration within a therapeutic subgroup, price mark-up over marginal costs, extent of vertical and/or horizontal integration, and market entry barriers, which are discussed next.

1.2.2 Barriers to Entry in the Pharmaceutical Market

Defining barriers to entry precisely is a controversial issue; several definitions have been proposed over time (McAfee, Mialon et al. 2003; Carlton 2005). Bain (1956) defined entry barriers as the set of technology or product conditions (economies of scale, product differentiation, and absolute cost advantages of established firms) that allow incumbent firms to earn economic profits in the long-run. Stigler (1968) modified the definition as "Cost of producing (at some or every rate of output) which must be borne by a firm that seeks to enter an industry but is not borne by firms already in the industry" (Bain 1956; Stigler 1968). Stigler emphasized the cost disadvantages of entrants relative to incumbents. Gilbert (1989) proposed a new definition focusing on the advantages of incumbents rather than cost disadvantages of entrants. According to Gilbert, an entry barrier is a rent that is derived from incumbency, i.e. the additional

profit that a firm can earn as a sole consequence of being established in the industry. Gilbert introduces sunk costs as a barrier to exit for the incumbent, which allows the incumbent to commit to a level of output, which in turn deters entry, earning the incumbent a rent (Gilbert 1989). Luís Cabral provides a broader, more general definition of barriers to entry as "the set of structural, institutional and behavioural conditions that allow incumbent firms to earn economic profits for a significant length of time" (Cabral 2010).

Barriers to entry could be structural or strategic (Besanko, Dranove et al. 2009). *Structural Entry Barriers* exist when the incumbent has natural cost or marketing advantages or when the incumbent benefits from favourable regulations. *Strategic Entry Barriers* are intentionally created by incumbent firms in the market, and include tactics to deter entry, which may constitute anti-competitive behaviour.

1.2.2.1 Structural Entry Barriers in the Pharmaceutical Industry

New entrants in the pharmaceutical sector are faced with several structural hurdles due to incumbents' first mover advantages, standards in market authorization and regulatory measures.

- Statutory/Regulatory Barriers to Entry: Patents that give the innovating firm the right to be the sole producer of a drug product for a maximum of 20 years is one of the most significant structural barriers. Pharmaceutical firms have to carry out significant preclinical and clinical testing to obtain marketing authorization.
- Economies of Scale: Pharmaceutical firms need a large budget base to sustain financial viability of R&D activities, satisfy regulatory standards of efficacy, safety (and cost-effectiveness in certain markets) and promote new products following commercialization. R&D scale economies emerge due to the need to maintain a portfolio of R&D projects as the risk of drug failure before commercialization is relatively high; only 1 in 4 drugs that go into clinical trials enter the market (Grabowski and Vernon 1990). In addition, significant sunk costs are incurred during the discovery process and clinical trials.
- Economies of Scope: Economies of scope are cost advantages that result from providing a variety of products rather than specializing in the production of a single product. Producing a given level of output for each product by a single firm may be cheaper than a combination of separate firms, each producing a single product at the

given output level. Pharmaceutical companies frequently share research and development expenses to bring new products to market through mergers. Sustaining diverse portfolios of pharmaceutical research projects that capture both internal and external knowledge spillovers helps pharmaceutical firms realize economies of scope (Henderson and Cockburn 1996).

- Advertising and Brand Loyalty: Brand loyalty is a significant barrier to entry, particularly in the generic sector. Although quality differences between generics and branded products are small, consumer or physician perceptions regarding the superiority of the brand may impede the take-up of generic drugs. Brand-name recognition increases the effective monopoly period for a drug product. Also, first-mover advantages may allow originator companies to maintain brand-name prices to remain above costs and dominate the market even after patents expire (Santerre and Neun 2010). Advertising and promotion enforce habitual prescribing at the physician level and constitute barriers to entry by increasing brand loyalty.

1.2.2.2 Strategic Entry Barriers in the Pharmaceutical Industry

Strategic entry barriers may include, but are not limited to, implicit collusion between firms (e.g. price fixing), predatory pricing (Lu and Comanor 1998), cross-subsidization, vertical integration, and building brand loyalty to limit erosion of market share by generics. Originator firms use several entry deterring strategies to block/delay the entry of generic competition. Such strategies include:

- Strategic patenting: Originator companies may create "patent clusters" by filing numerous additional patents for the same medicine to delay or block the market entry of generic medicines. Patent clusters make it more difficult for generic competitors to see whether they can develop a generic version of the original medicine without infringing one of the many (new) patents of originator companies.

- Patent settlements: Patent disputes between originator and generic companies can result in the restriction of generic manufacturer's right to market its medicine. Both in the US and EU, significant number of settlements include a direct payment from the originator to the generic company, a license, or a distribution agreement.

- Authorized generics: An authorized generic is a pharmaceutical product that is marketed by a brand company (or through a subsidiary or licensed in return for royalties) but is relabeled and marketed under a generic name (Banait 2005). Authorized generics in the US do not have to abide by the 180-day market exclusivity provision

granted to the first generic on the market and result in a substantial reduction of the economic benefits of the six-month exclusivity period that drives the first generic entry.

- Product hopping/switching: Branded companies may prevent substitution to lower-priced generics by introducing new patented products with minor or no substantive improvements and switch customer demand to the new products.

Finally, some types of barriers can be both structural and strategic depending on the particular situation. Statutory/regulatory barriers, for example, could be either structural or strategic depending on whether incumbent firms played an active role in persuading the government to create them. Similarly, although sunk costs are typically structural barriers, they could be considered strategic if incumbent firms strategically integrate vertically and enhance potential entrants to do the same thing (OECD 2007). The thesis will dominantly incorporate the impact of structural barriers to entry as they are more easily quantifiable compared to strategic barriers to entry. In particular, the main focus will be on regulation as a strategic barrier to homogenous entry in different markets and on launch strategies developed by pharmaceutical firms as a response to price regulation.

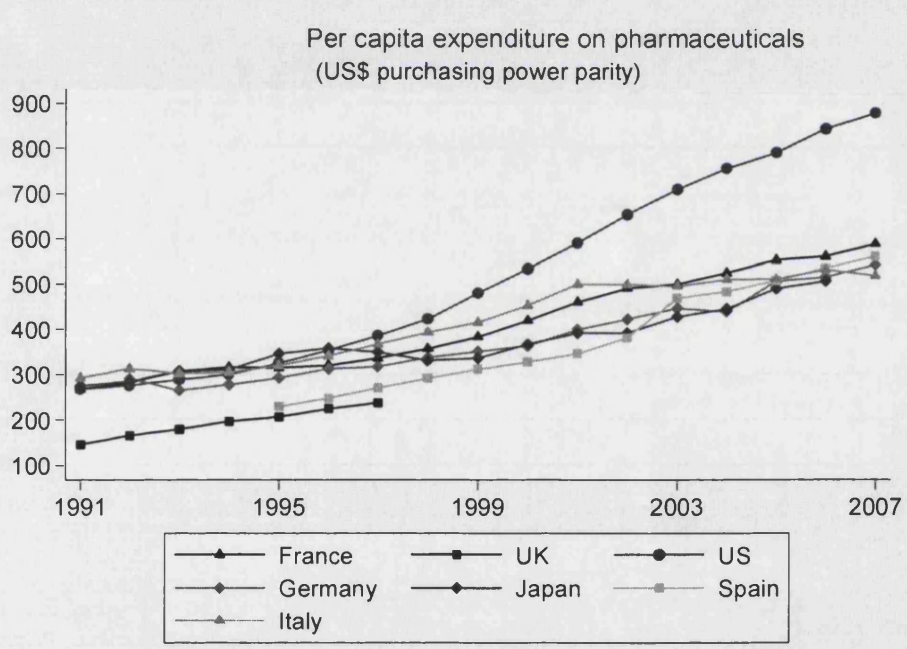
To sum up, government intervention in the pharmaceutical market is justified by economic theory to correct inefficiencies associated with market failures such as moral hazard, informational asymmetries and lack of competition due to exclusivity rights granted by patents (McPake, Kumaranayake et al. 2002). Regulation affects the pharmaceutical industry on several levels: IP rights; R&D and product registration regulations; price and reimbursement regulations (Gassmann, Reepmeyer et al. 2008). Pricing and reimbursement (P&R) controls are broadly used to account for lack of competition and limit moral hazard. Although theory suggests that regulation is potentially welfare enhancing, designing the optimal structure of P&R regulations is not simple and relies on positive empirical evidence to inform policy-making. Section 1.3 will introduce an overview of various P&R mechanisms used across the major OECD markets.

1.3 From Theory to Practice: Pharmaceutical Price & Reimbursement Regulation

1.3.1 Rising Concerns over Cost-Containment

Rapid growth in healthcare expenditure has become a universal policy issue in industrialized countries especially after 1998. The increase has been particularly dramatic in the US market that currently faces the globally highest healthcare expenditure relative to GDP (17% of GDP in 2007, as compared to the EU average of 12%) (see Figure A.1 in Appendix A). Health spending per capita over 1997-2007 has grown in real terms by 4.1% annually on average across the OECD. Average economic growth over the same period was 2.6%, which has resulted in an increasing share of economic resources to health in the majority of the countries (OECD 2009).

Figure 1.1 Total expenditure per capita on pharmaceuticals and other medical non-durables, US$ purchasing power parity (Source: OECD Health Data, 2009)



The percentage share of pharmaceutical expenditures in total healthcare expenditures over the past decade ranged from 13-15% in the free-priced markets (US, UK and Germany) to about 20% in more stringent price control markets such as Italy, Spain and Japan (OECD 2008). Although the percent share of pharmaceuticals has decreased as a response to stringent controls in Italy and Spain (see Figure A.2 in Appendix A), pharmaceutical expenditure per capita has invariably increased in absolute terms over the past decades in all major pharmaceutical markets, with considerable variation across

countries due to differences in pharmaceuticals pricing policies and consumption patterns (Figure 1.1).

The growth in drug expenditures exceeded the growth in GDP during 1980-2005 (OECD 2008). Ageing populations, rising prevalence of chronic conditions, adoption of new and expensive technologies, treatment of new disease areas and emergence of life-style drugs have been the main drivers of rising pharmaceutical expenses. There has been a shift to more complex products with higher clinical trial costs; the number of trials required to support a new product has risen due to the need for comparative trials (Charles River Associates 2004).

Rising pharmaceutical expenditures in the last decades have increased the pressure on policy makers to adopt supply- and demand-side regulations on a wider scale to curb the growth while ensuring equity and efficiency in pharmaceutical spending in the major OECD markets. Cost-containment policies employed include direct or indirect price controls, reference pricing systems and cost-sharing to moderate demand by increasing patients' price sensitivity, generic substitution, reimbursement restrictions to products in positive lists and/or reimbursement exclusion of products on negative lists, physician prescribing guidelines and budgetary controls. The success in the implementation of different pharmaceutical pricing and reimbursement schemes varies among countries depending on prescribing habits, industrial policies, and public health measures (Mossialos, Walley et al. 2004a; Mossialos and Oliver 2005).

The following sections provide an overview of different pricing and reimbursement controls. Appendix A.3 provides more detailed, country-specific pricing and reimbursement information on the biggest six pharmaceutical markets (US-EU5 comprised of the US, UK, Germany, France, Italy and Spain). The US-EU5 accounts for a major proportion of the global pharmaceutical R&D as well as more than 70% of the $1.5 bn global pharmaceutical retail sales. Hence, pricing and reimbursement policy implications in these markets are substantial for the global operations of the drug industry (Datamonitor 2009; EFPIA 2009).

The Transparency Directive (European Directive 89/105/EEC) is the main legal agreement in the area of pharmaceutical P&R in the European Union. Although the directive aims to ensure the transparency of P&R procedures established by Member States (MS), each MS has the competency to determine the prices and reimbursement levels on a national or regional basis. This has resulted in a significant fragmentation in

P&R policies within the EU. In practice, national pricing and reimbursement regulation mainly focuses on the price level ex-factory (manufacturer sale price), the reimbursement level (amount paid by public funds) and restrictions on the (proxy) demand-side (doctors, pharmacists, patients).

1.3.2 Pricing Controls

Pricing policies are broadly classified as free pricing and price control. Under a free pricing policy, manufacturers or wholesalers may freely set pharmaceutical prices; in contrast, under price control prices are determined by the authorities. Price control is usually exercised through statutory pricing, price negotiations in the outpatient sector and public procurement in the inpatient sector. The most common pricing policy across the OECD is statutory pricing, whereby the price is set on a regulatory basis through laws or decrees. One of the most widely used approaches is to define price caps through external referencing. In external price referencing, prices (usually average prices) in a set of reference countries are used to determine a cap for the local price. In many countries the number of reference countries is 5 or less; only Austria and Belgium refer to all other EU Member States (Vogler 2008).

Price negotiations involve bargaining, negotiation to determine drug prices between the manufacturer and the government authority (Social Health Insurance or National Health Service). Under public procurement, the state (e.g. hospitals) purchase pharmaceuticals based on a tendering procedure that grants the contract to the best tenderer (pharmaceutical company or importer). Hospitals generally obtain large-scale discounts on drugs due to public procurement and/or direct negotiations with the manufacturers. Prices of hospital pharmaceuticals, therefore, tend to be lower than in the outpatient sector.

In the majority of the markets, prices are controlled in the outpatient sector and the control is limited to reimbursable pharmaceuticals. Manufactures/importers are usually free to set the price for non-reimbursable pharmaceuticals, usually comprised of OTC products. Belgium, Greece and Turkey regulate prices of all pharmaceuticals whereas Netherlands and Portugal apply price control for prescription-only (ethical) drugs. In Germany, there is free pricing at the ex-factory price level but mark-ups are regulated at the distribution level. UK has no direct price control but prices are indirectly affected by the Pharmaceutical Price Regulation Scheme (PPRS) that sets limits on the maximum

profits manufacturers can make on their sales. However, there are ongoing discussions about replacing the PPRS system with a Value Based Pricing (VBP) when the current PPRS expires in 2014.

Another common pricing procedure is internal price referencing, which compares prices of identical or similar pharmaceuticals within a country. Internal price referencing is applied if a reference price system is in place for reimbursement purposes. Therefore, it applies mostly to reimbursable pharmaceuticals, but may also include off-patent products and/or parallel imported pharmaceuticals. A less often used pricing approach is cost-plus pricing which is based on a proof of certain costs (production cost, R&D cost etc) plus a granted mark up. Greece, for example, uses cost-plus pricing to set prices of locally produced pharmaceuticals. Other markets that apply several pricing criteria, e.g. Finland, may consider costs while setting price.

Prices of generics (bioequivalent drugs of a branded original pharmaceutical with an expired patent on the active ingredient) are considerably lower than the original product. Additional measures may aim to reduce the prices of the second and further generics. Special P&R measures apply to parallel imports in countries where their share is important. In Sweden, for example, substitutable pharmaceuticals (including generics and parallel imported pharmaceuticals) are grouped together within the system of mandatory generic substitution. A price lower than or equal to the highest price within a group of substitutable pharmaceuticals is accepted without further investigation.

At the distribution level, majority of the countries have statutory wholesale and pharmacy mark-ups, either a linear mark-up or a regressive scheme. Finland, Netherlands, and Sweden apply no statutory wholesale mark-up. Similarly, pharmacy mark-ups may in addition involve a fixed fee (e.g., Netherlands) or a fee-for-service remuneration (the UK). On top of the wholesaler and pharmacy mark-ups additional VAT (value added tax) is charged.

1.3.3 Reimbursement

Eligibility for reimbursement, i.e. full or partial coverage of the purchasing cost by a third party payer, can be product-based (Austria, Belgium, Finland, France, Germany, Italy, Netherlands, Poland, Portugal, Switzerland, UK), disease-based (for some diseases in France and Portugal), population group-based (Turkey) and consumption-

based (Sweden). Eligibility for reimbursement and the reimbursement rates depend on the product in most countries.

Countries have reimbursement lists that define drugs to be included into reimbursement (positive lists) or drugs to be excluded from reimbursement (negative lists). Inclusion into a positive list is usually based on the therapeutic benefit offered by the drug in comparison to existing alternative products. Most countries have positive lists; however, Germany and the UK use negative lists.

The reimbursement price is the maximum amount paid by the third party payer. In most countries products are partially reimbursed (see Table A.3 in Appendix A.3.2 for a summary table of pharmaceutical P&R regulations in the EU5). Only in Austria, Germany, Italy, the Netherlands and the UK all reimbursable pharmaceuticals are 100% reimbursed (but further co-payments are possible due to a reference price system or in the form of prescription fees). Patients may be required to co-pay for reimbursable pharmaceuticals out-of-pocket or through complementary insurance. In Austria, Finland, Poland, the UK and in some regions of Italy patients have to pay a fixed fee for Rx pharmaceuticals (fixed co-payments/ prescription fees).The most common out-of-pocket payment for pharmaceuticals is the percentage co-payment. Deductibles, a fixed amount that the patient has to pay for a defined period before the cost is fully or partially reimbursed, is found in consumption-based reimbursement schemes such as in Sweden.

Under a reference price system (RPS), interchangeable pharmaceuticals are grouped into a "reference group" at the chemical substance (ATC5) level as in Italy and Portugal, or at the therapeutic (ATC4 or above) level as in Germany, Netherlands and Poland. Usually, off-patent products are considered for inclusion in a reference price system. In Germany, on-patent brands are included into the reference groups. A maximum reimbursable amount, the reference price, is determined based on the prices of products in the reference group. The methodology used to determine the maximum reimbursable amount differs across countries. The patient pays the difference between the reference price and the actual pharmacy retail price, in addition to any fixed co-payments or percentage co-payment rates.

Additional out-of-pocket payments may be incurred as prescription fees, percentage co-payments and deductibles. Percentage co-payments for partially reimbursed drugs are the most common form of out-of-pocket payments. Germany was the first country to

introduce RPS in 1989; the Netherlands and Sweden followed in the early 1990s. Sweden, however, abolished the RPS in 2002 and established a system of obligatory generic substitution. In Sweden, substitutable pharmaceuticals are clustered. Prices not exceeding the highest price within such a group are automatically accepted for reimbursement. Belgium, France, Italy, Portugal, Turkey and Greece all introduced RPS after 2000.

Most countries grant 100% reimbursement to inpatient pharmaceutical expenditures and the expenses are borne by the institutions that fund the hospitals. In addition to the above mentioned cost-containment mechanisms, measures for rational drug use have been adopted. These include prescription guidelines, physician budgets, generic promotion through generic substitution and generic prescribing, pharmacoeconomic evaluations, prescription and consumption monitoring.

1.3.4 Effects of Pharmaceutical Price & Reimbursement Regulations

According to Stigler the central task of the theory of economic regulation is to explain the form of regulation and the effects of regulation upon the allocation of resources (Stigler 1971). According to the public interest theory, government policies are aimed at increasing efficiency and equity to promote the general interests of the society as a whole. In the presence of market imperfections markets fail to allocate resources efficiently, i.e. marginal social cost does not equal marginal social benefit for a given distribution of income. The government intervenes to ensure distributional justice (equity) and correct market failures in the pharmaceutical market by affecting producers' and suppliers' choices regarding pricing and prescription behaviour.

Government initiatives to correct market failures may result in worse outcomes. The public sector analogy to market failure is known as "government failure" and occurs when a government intervention causes a more inefficient allocation of goods and resources than would occur without that intervention. On the other hand, government's failure to intervene in a market failure that would result in a socially preferable mix of output is referred to as "passive government failure" (Weimer and Vining 2005; Stiglitz 2009).

Government failure and market failure can coexist. Public/industrial policy should be informed not only by an understanding of market failure but of government failure as

well. The theory of government failure however is not well-developed enough to allow to predict the consequences of specific government interventions. Empirical evidence, therefore, is extremely important to analyze the contribution of market and government failure to inefficiencies in the market.

The impact of regulation in the pharmaceutical industry has been analyzed from several perspectives. A significant body of literature investigates how regulation affects pharmaceutical prices and competition, R&D and sustainability of pharmaceutical innovations, patient access to medical treatments and healthcare cost-containment. However, these studies have largely been partial analysis looking at the impact of regulation and not the form of optimal regulation.

Isolating the impact of each measure has proven difficult due to differing unmet healthcare needs and healthcare system structures as well as simultaneous adoption of several measures. Although the overall effect of each pricing and reimbursement measure on social welfare remains an unclear contentious issue in the public policy arena, major stylized facts that emerge from the literature are summarized in the following section.

1.3.4.1 Effects on Pharmaceutical Firm Strategies

Revenues, R&D Investments and Innovation

According to economic theory firms invest in capital up to the point where the expected marginal efficiency of investment in R&D is equal to the firm's marginal cost of capital (Vernon, Golec et al. 2006). P&R regulations affect the optimum R&D level in several ways. Majority of the regulations reduce pharmaceutical firm revenues and expected returns to R&D, with the direct price controls having the biggest impact (Vernon 2003; Sood, de Vries et al. 2009). Empirical research by Grabowski and Vernon (2000) shows that expected returns and cash flow are important determinants of pharmaceutical R&D. Given that sales revenue comprises the primary source of R&D financing[3], price regulation results in reduced pharmaceutical profitability and R&D spending (Grabowski and Vernon 2000).

[3] External funding sources such as private equity or new debt is available only at higher costs due to the risk premium required by investors/lenders

Price regulations reduce the internal rate of return of R&D projects which results in reduced market entry for innovative drugs as fewer projects can compensate for the cost of capital (Giaccotto, Santerre et al. 2005; Golec, Hegde et al. 2008). In addition, P&R regulations may also reduce expected present value of cash flows by delaying market access and reducing the duration of market exclusivity and effective patent protection.

Entry Strategies

How regulation affects timing of entry of pharmaceutical technologies is a question still open to empirical investigation[4]. Although recently several studies have analyzed the impact of regulation on the timing of new molecule launches, existing evidence is limited, particularly for the off-patent sector. Pharmaceutical price regulation results in delays in market access for new chemical entities as well as reduced extent of entry. Coutries with a stringent regulation of entry but with relatively little price regulation (US, UK) tend to be launched in more foreign markets (Thomas 1994). Pharmaceutical companies often aim to launch their products first in markets with highest market size and highest prices to influence prices in subsequent markets with price control upwards (Danzon, Wang et al. 2005; Kyle 2007; Danzon and Epstein 2008).

Pharmaceutical regulation also affects the entry of generic competitors. Danzon and Chao (2000) find empirical evidence that generic market shares are lower in prices with price regulation (Danzon and Chao 2000a). Different approval processes and the national nature of patent rights in Europe have created a major barrier to generic penetration in the EU. The requirement for generic products to receive approval in each separate state has delayed the diffusion of generics cross-nationally. The mutual recognition process aimed to facilitate this in 1995. Differences in supplementary protection certificate expiry dates can further delay generic entry. Another major issue before generic penetration in the EU has been the late introduction of patent laws in several EU countries such as Spain, Italy and Portugal. The presence of unregulated copy products has created distrust on the demand-side. In general, markets with higher branded prices, i.e. less price regulation, are more favourable to generic entry because

[4] In the healthcare setting, a clear distinction is drawn between adoption and diffusion although these terms tend to be used more interchangeably in general. Adoption is defined as the first contact of the physician with the innovation. In the context of this thesis, adoption is used to refer to the first launch date of a given patent-protected molecule or its generic copy. Diffusion, on the other hand, depends on the rate of prescription of a new drug by physicians over time (Costa-Font, Courbage et al. 2009). Timing of adoption in this thesis will be analyzed at the market-level for each country.

high prices increase both the incentive for payers to use generics and the profit potentials for generic players (Schulz 2004).

Additional requirements with respect to pricing and reimbursement delay generic entry (DG Competition 2009). The inquiry of the European Commission into the competitiveness of the pharmaceutical industry in 2009 has identified that generic entry in the EU is delayed due to the impact of regulation (lengthy marketing authorization, pricing and reimbursement procedures) and company behaviour (patent application and enforcement strategies).

There are few studies in the literature on generic entry outside the North American market that will shed light on the impact of different regulations on generic entry. Evidence from the Swedish and Spanish markets shows that expected profits/revenues are associated with higher generic entry in a regulated environment. A shorter patent protection period for the branded product resulted in a higher number of generic entrants in the Swedish market (Rudholm 2001).

Reference pricing can restrain generic entry by depriving generic firms of their main advantage, lower prices compared to the brand-name alternatives (Moreno-Torres, Puig-Junoy et al. 2007). Evidence from an earlier Swedish market by Ekelund (2001) confirms that the reference price system on average decreases the probability that generics are launched (Ekelund 2001).

Competition and Pricing Strategies

The evidence on the impact of P&R regulations on pricing strategies is relatively limited. Price regulation of branded drugs arguably undermines price competition generated by generic firms and results in higher generic prices in price-regulated markets than in the US (Danzon and Chao 2000b; Graham 2001). According to Frank and Salkaver, the demand for brand-name prescription drugs is composed of two segments: a cross-price-sensitive segment that is sensitive to prices of generic equivalents and a loyal segment whose demand is unaffected by the price of generic substitutes. In a free-priced market, branded manufacturers may opt to target the brand-loyal segment and increase prices following patent expiry.

The higher the price difference between the branded and generic alternatives, the higher is the probability that the price sensitive segment switches to generic alternatives. Price

regulation pushes prices of branded medicines downwards and decreases branded-generic price differential, undermining the competitive advantage of generics. Similarly, in price controlled markets manufacturers usually cannot increase the price to the brand-loyal segment.

The impact of *reference pricing* (RP) on prices and competition depends highly on the way clusters are defined, how reference prices are set and whether generic substitution exists (López-Casasnovas and Puig-Junoy 2000). In general, reference pricing pushes firms to lower prices resulting in narrow price ranges within a cluster. Savings due to RP systems have been high in markets with high priced markets with large price differentials across drugs in the same reference group and a well-developed generic sector such as in Germany (López-Casasnovas and Puig-Junoy 2000). Savings have remained more modest in markets such as Spain and Italy where the generic market is not very developed and prices are relatively low (Puig-Junoy 2004). *Generic substitution* contributes to a reduction in drug prices and slows down the growth of pharmaceutical expenditure (Buzzelli, Kangasharju et al. 2006) (Andersson, Bergström et al. 2007).

Parallel trade (arbitrage) and external reference pricing have increased the dependency of prices between different markets. This precludes firms from setting prices individually in each market. Pricing decisions have to consider interactions between country prices and the profit knock-on effects across markets. There is empirical evidence which suggests that prices in the EU have started to converge as a result of strategic pricing by pharmaceutical firms (Kyle 2007).

1.3.4.2 Effects on Public Spending and Welfare

The results regarding policy interventions on public spending or welfare are not easy to interpret because measures are usually applied contemporaneously and isolating the impact of one measure may be difficult.

A recent study by Lakdawalla et al (2009) measures the impact of different policy choices on current and future generations of Americans and Europeans by using a global micro-simulation model of health and mortality. The model focuses on price controls and copayment reductions. Their main finding is that copayment reduction is a robust and welfare-improving policy whereas price controls offer a relatively modest benefit (Lakdawalla, Goldman et al. 2009).

Cost Sharing

Cost-sharing has been accepted as an effective tool in increasing price sensitivity, reducing moral hazard and thus health expenditures (Winkelmann 2004; Grabka, Schreyögg et al. 2006; Li, Guh et al. 2007). The reduction in demand through cost-sharing, however, falls more heavily on the poor and chronically ill individuals. The RAND Health Insurance Experiment in the US that was conducted during 1974-1982 provides the only randomized study of health insurance and the impacts of different co-payment levels. This experiment showed that cost sharing reduced both necessary and unnecessary medical care, however, with possible side effects due to the decrease in the consumption of medical services (Brook, Ware et al. 1983; Brook, Ware et al. 1984).

Reference Pricing

In France, Germany, Italy and Spain reference pricing is used as a cost-sharing means for reimbursed pharmaceuticals. Although prices tend to drop following inclusion of products into clusters, the exact impact of reference pricing systems on cost-containment depends on the clustering and reference price mechanisms as well as other incentives in the system. Several studies conclude that RP has failed to control the aggregate growth of pharmaceutical expenditures (Pavcnik 2000; Danzon 2001; Ioannides-Demos, Ibrahim et al. 2002) (Kaló, Muszbek et al. 2007). Net savings on total expenses depend on by how much utilization of other health care services increases due to introduction of RP and the budget impact of the pharmaceutical sub-segment to which RP is applied (López-Casasnovas and Puig-Junoy 2000; Puig-Junoy 2004). Also, firms may increase the prices of other products not subject to RP (Mestre-Ferrandiz 2003).

Savings due to RP systems have been high in markets in high priced markets that have large price differentials across drugs in the same reference group and a well-developed generic sector such as in Germany (López-Casasnovas and Puig-Junoy 2000). The existence of generic competition and introduction of RP in Germany fuelled a price decrease (Pavcnik 2000). Savings have remained more modest in markets such as Spain and Italy where the generic market is not very developed and prices are relatively low (Puig-Junoy 2004).

Generic Substitution

Buzzelli et. al. (2004) study the impact of generic substitution on pharmaceutical prices and expenditures in OECD countries (Buzzelli, Kangasharju et al. 2006). On average, prices were reduced by 3.1% following the implementation of generic substitution, controlling for the growth rates in prices, time trend, country-specific differences in prices, population age structure, and income levels. The point estimate for reduction in expenditures, however, is 1.6% and not statistically significant, which suggests that consumption of pharmaceuticals increased as prices were reduced (Buzzelli, Kangasharju et al. 2006). The introduction of generic substitution in Sweden shifted the increasing expenditure trend, both in patients' and society's expenditures, to a decreasing trend, which shows that generic substitution has contributed to a reduction in the growth of pharmaceutical expenditure (Andersson, Bergström et al. 2007).

Haas et al (2005) estimated savings of approximately 11% of total drug expenditures ($5.9 bn) if a generic had been substituted for all brand-name outpatient drugs in 2000 (Haas, Phillips et al. 2005). Similarly, Simoens and De Coster (2006) estimate that substitution of top 10 originator medicines by sales would have generated savings in public expenditures by at least 20% in some EU countries (Simoens and de Coster 2006).

Parallel Trade

Although the benefits of parallel trade mainly accrue to intermediaries, parallel trade across the EU has resulted in savings in the pharmaceutical expenditure through introduction of lower-priced products and increased competition (Kanavos and Costa-Font 2005). For example, direct savings for Germany and the UK have been estimated to be 0.4% and 1.7% respectively. Several other studies also observe significant cost-containment in the EU with indirect competitive effects through reduced prices (West and Mahon 2003), (Ganslandt and Maskus 2004). On the other hand, considering the negative effect parallel importing has on the pharmaceutical industry the total negative effect of parallel importing on the UK economy has been estimated to be more than £290 million (Thomas 2008). However, cost-containment potential due to parallel trading is decreasing as a result of pharmaceutical company strategies to reduce price differentials across countries and other non-price strategies such as the launch of differentiated products across the EU (Enemark, Møller et al. 2006).

1.4 Thesis Background

This thesis discusses how to model the effect of regulation on the adoption of new pharmaceutical molecules and first generic competition. The analysis draws upon sales ($) and price ($/SU[5]) data from IMS[6],[7] during 1998-2008 in a panel of 20 countries, 19 of which are within the OECD. Adoption of pharmaceutical technologies is modelled using time to event analysis (survival analysis), whereby failure times are defined by the time elapse between the global launch date of molecules (global adoption) and local launch dates (local adoption) of molecules in individual countries. Discrete-time survival analysis is carried out controlling for regulation, market attractiveness, molecule and firm heterogeneity.

From an economic perspective it is important to analyze relative launch delays across countries because delays affect both consumer welfare and industrial welfare, and have implications for industrial and public health policy. Delayed access to new drugs compromises health outcomes and quality of health care (Schoffski 2002), shifts volume to older molecules of lower therapeutic value (Danzon and Ketcham 2004) and increases expenditures on other forms of medical care (Kessler 2004; Wertheimer and Santella 2004). Innovative medications offer consumer benefits through fewer work days missed and lives saved (Lichtenberg 1996; Lichtenberg 2003a; Hassett 2004; Lichtenberg 2005). Delays hit the pharmaceutical industry through reduced market exclusivity periods, lower returns to R&D and shrinking pipelines.

Timely generic adoption and uptake following the expiry of originator patents and additional exclusivity protections enhances efficiency and competition in the drug market. Generics are by definition bioequivalent to originators, and constitute perfect substitutes on objective quality grounds. Significant cost-advantages in product development and barriers to entry allow generics to compete based on price, which makes generics cost-effective alternatives to off-patent medicines that can curb expenses effectively. Freed resources can be used to fund and incentivize the development of new more effective pharmaceutical technologies. Generics may also affect consumer welfare through increased affordability and access.

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[5] IMS standard units

[6] Intercontinental Medical Statistics, www.imshealth.com/

[7] Data was collected at Merck Sharp Dome, UK.

I argue that price regulation slows down the adoption of pharmaceutical technologies, both for new molecules and generics, by increasing structural barriers to entry. Lower prices result in lower profits, reduced incentives to entry and potentially lower competition and higher market concentration. Firms are optimizers of future global revenue inflow. Price linkages across markets result in reduced or delayed launch in low-priced markets, or result in narrower price bands across countries.

1.4.1 Contributions of the Thesis

The thesis contributes to the economics of regulation literature by providing positive empirical evidence on the adoption of pharmaceutical technologies for human use. Theory does not tell us much as it depends on precise market structure, number of firms, and specific regulation in individual markets. Additional major contributions of the thesis can be summarized as follows.

i) Data

- Recent and comprehensive IMS Data: This thesis makes use of recent IMS price, volume and launch timing data in the main OECD markets during 1999-2008. IMS data is one of the most reliable pharmaceutical sales and price data available, and is widely used both academically and commercially. IMS data is validated annually and has positioned itself as one of the most reliable sources of healthcare market data.

- Country and Molecule Set: The dataset used covers 20 markets[8]. As mentioned before, only the US-EU5 account for more than 70% of the global pharmaceutical sales and for the majority of the global R&D. The set of molecules comprises all 14 different ATC1 categories (see Table A.2). The thesis contributes by adopting stricter criteria for the global potential of molecules, e.g. the analysis for adoption of innovation considers molecules that have launched in more than 10 markets and the analysis of first generic adoption considers molecules that have launched a generic both in the US and UK to avoid bias due to one-market molecules. The choice of the

[8] Australia , Austria, Belgium, Canada , Finland , France, Germany , Greece, Italy, Japan, Netherlands, Poland, Portugal, South Africa, Spain, Sweden, Switzerland, Turkey, the UK, and the US

country and molecule set in the regressions therefore increases the importance and relevance of results from a policy perspective.

ii) Methodological

- Multivariate Survival Analysis: In terms of statistical methods first analyses in the literature used less sophisticated methods such as ordinary least square regressions, and Pearson correlation coefficients. The assumed normality for time to an event is often an unreasonable assumption. Time-to-event is non-negative, non-symmetric and usually positively skewed. Linear regression approaches are not robust to these violations (Cleves, Gould et al. 2008). In addition, time-to-event is censored if the survival time of some objects is not observed before the termination of the observation period. Failure to take censoring into account can introduce serious bias in estimates of the distribution of survival time and factors that affect survival time.

  Binary response models (probit) have been estimated by defining a threshold period for the definition of success (i.e. launch before a pre-determined period) (Heuer, Mejer et al. 2007). Such an approach results in severe loss of timing information. Methodologically few analyses have adopted multivariate survival analysis methods that incorporate more detailed time information and account for the censoring in the survival data. Since the failure times in the IMS data are interval censored, I use discrete-time survival analysis methods to specify the hazard of launch.

- Identification of Regulation and Competition: The majority of prior studies use treatment dummies to account for the impact of regulation. Price control treatment dummies cannot capture the diversity and complexity of prices across different therapeutic groups and over time. This thesis made use of product level price information that allows controlling for changes over time as well as variation across different therapeutic areas. Only few studies have made use of price and volume information to account for heterogeneity in policy measures across markets (Danzon, Wang et al. 2005; Danzon and Epstein 2008). Following the approach by Danzon (2008), I proxy for the impact of price regulation through average lagged competitor prices in the same therapeutic subgroup controlling for country and time fixed effects. Use of lagged expected prices also aims to avoid endogeneity of price and the launch decision.

Prior studies have primarily used the number of competitor molecules as the main proxy of competition. This approach, however, gives equal weight to each competitor. Different from prior studies in the literature, the impact of competition was investigated using the Herfindahl Hirschman concentration index for molecule sales in the same ATC4 in Chapter 3 and the sales of generic firms in ATC4 in Chapter 4.

- Incorporation of Molecule and Firm Heterogeneity: Only a few studies have attempted to disentangle the effects of firm and molecule characteristics in estimating the hazard of launch. Omission of such variables could significantly bias parameter estimates, and effect standard errors as well as hypotheses tests. All empirical analyses control for market structure, firm and molecule characteristics on the probability of launch to estimate coefficients more precisely. Also, errors were clustered at the molecule-country level to account for potential autocorrelation over time.

- Checks for robustness and multicollinearity: Substantial robustness checks were carried out to identify how sensitive parameter estimates are to the regression methodology and duration specification. Robustness checks were carried out by testing alternative proxies for variables and estimating the model with different regression models (Cox, cloglog and logit). Duration dependence was controlled for both parametrically and non-parametrically to detect possible misspecification errors. Multicollinearity of regressors was investigated by calculating variance inflation factors to choose better model specifications that would not result in inflated parameter variances.

iii) Contents

- First Analysis of Evolutionary Trends: The thesis provided the first comparison of launch lag trends across markets and different time periods during 1960-2008. I also tested for the impact of the two main regulatory changes using a quasi-experimental framework with difference-in-differences analysis as well as fixed and random effects Cox proportional hazards model.

- Evidence on Adoption of Innovation: I extend the work by Danzon and Epstein (2008) which also provided an analysis of launch times using price and volume information. Their work has been criticized for not inlcluding globally important

molecules (Garattini and Ghislandi 2007). I define more stringent criteria to select the molecules; only molecules that diffused to at least 10 markets were included in the analysis of timing of new molecule adoption. I also employ more extensive controls for firm, molecule and therapeutic subgroup competition effects to isolate the impact of these variables, potentially reducing the variability in the parameter estimates.

- Evidence on Timing of Generic Entry: Evidence for timing of generic entry is extremely limited. This is the first study that employs substantial cross-country data to examine timing questions in the generic sector. No prior analysis has used molecule and market-specific price information for timing of launch analysis in the off-patent sector.

iv) Results

The analysis in this thesis clearly suggests that pharmaceutical corporations launch strategies are highly responsive to changes in the regulatory landscape and the legal transaction costs of entry. The thesis provides robust evidence that price regulation is associated with delays both locally but also internationally due to price linkages across markets. The evidence presented here indicates that firms behave strategically in their launch decisions and commercialize their products first in high-priced markets. There is an indication that firms are launching products within a narrower price range in the European market to reduce the impact of price and profit spillovers across Member States. Controlling for delays in the adoption of new molecules, generic launch also suffers from price controls. This is mainly because price controls depress originator prices and the price mark-up between originators and generics, reducing the incentives for generic entry.

The comparison of cloglog and cox models indicates that cloglog is the preferable specification with the interval-censored failure times in the IMS data. Logit and cloglog estimates, on the other hand, gave very close parameter estimates. Overall, parametric and non-parametric duration specification result in similar estimates but the parametric approach is preferable in some specification due to the parsimony in parameter estimates compared to the non-parametric speficiation.

The next section provides an overview of the organization of the thesis and the main hypotheses tested in each empirical chapter.

1.4.2 Organization of the Thesis and Main Research Questions

The overarching purpose of this thesis is to provide a positive economic analysis of how pharmaceutical price regulation affects adoption of pharmaceutical technologies, both for innovative new molecules and generic competition, during 1999-2008 across the main OECD markets relative to the market where the first global launch occurs. The thesis will not address the question of whether or not price regulation improves overall social welfare. Quantitative analysis of this nature is beyond the scope of the thesis. However, a better understanding of drug adoption to price regulation through positive economic analysis will help inform the debate over price controls, free trade in pharmaceuticals and the static-dyanamic efficiency trade-off.

The thesis is comprised of three empirical chapters introduced below together with the research hypotheses in each chapter.

Chapter 2

Chapter 2 is an exploratory analysis that quantifies the delays in the launch of new molecules and generics across markets and different periods. This chapter investigates the evolution of pharmaceutical corporations' launch strategies as a response to changes in regulation. The analytical framework is defined using two regulatory changes that reshaped the barriers to entry substantially: the US Hatch-Waxman Act in 1984 and the establishment of the European Medicines Agency (EMA, abbreviated as EMEA before 2010) in 1995.

This chapter considers potentially global molecules (molecules that launched in both the UK and the US) and truly global molecules that launched in all of the 20 countries within the IMS data used for the analysis. Non-parametric survival analysis is carried out to calculate the mean and median survival times. Failure times of each molecule-country pair are defined as the time difference between the first global launch date and local launch date of new molecules or first generic product of each molecule. Kaplan-Meier survival estimates are calculated for each market in three times using molecules (and in the second section generics) that first launched globally during the following periods: 1) 1960-1984; 2) 1984-1995; and 3) 1995-2008. Finally, difference-in-difference (DiD) analysis is carried out to assess whether policy changes in 1984 and 1995 had a significant effect on the speed of adoption.

Hypotheses tested in Chapter 2 are as follows:

H 2.1: Do pharmaceutical corporate launch strategies respond to changes in the regulatory environment?

It is expected that pharmaceutical firms will respond to regulatory changes that reduce transaction costs and improve efficiency and transparency of market authorization procedures. The Hatch-Waxman act has restored the patent term for innovative molecules and enabled generics to enter the market without having to carry out expensive clinical trials. The establishment of the EMEA has also reduced transaction costs by harmonizing market authorization requirements in a fragmented EU market.

H 2.2: What is the trend in the differentials in drug adoption over time?

It is expected that drugs diffuse to markets faster over time as result of international harmonization of market authorization regulations and globalization of pharmaceutical corporations. Also, Bolar provisions granted to generics in the US and EU have substantially reduced structural barriers to generic entry over the past decades.

H 2.3: What is the impact of centralized authorization on relative delays in new molecule launches across the main European pharmaceutical markets?

Establishment of the EMEA is expected to have reduced the transaction costs, and thus, differential delays in adoption across the EU for centrally approved molecules.

Kaplan-Meier estimates for mean survival time show that pharmaceutical corporations' launch strategies have responded to regulatory developments and changes in barriers to entry. The US faced a significant drug lag in comparison to European markets following the 1962 Kefauver Harris Amendments that introduced stringent market authorization requirements for new pharmaceutical products. This delay was closed after the 1984 Hatch-Waxman Act that introduced new financial incentives for innovative drugs by restoring the patent term lost during drug development. Recent estimates show that although a centralized market approval in Europe narrowed the differentials in timing of launch across countries, there still exists a pattern of delay across Europe due to

differences in local pricing and reimbursement regulations (and potential profit spillovers as discussed in Chapter 3).

New molecules launch first in higher-priced European markets as a result of threat of arbitrage and price dependency created by external reference pricing. A surprising finding in Chapter 2 is that Japan, the second largest pharmaceutical market, exhibits substantial delay in the adoption of new pharmaceutical technologies. The impact of price controls suggests a similar delay pattern in the launch times of first generic products. DiD estimates indicate faster adoption both for new molecules and generics in the US following the Hatch-Waxman Act in 1984; which suggests that the Act has been successful in restoring incentives for innovative molecules while stimulating the generic sector. DiD estimates for the impact of the establishment of the EMEA in the EU indicate that adoption of new molecules is significantly faster; however, the impact of the EMEA on generic adoption was not significant.

Chapter 3

Chapter 3 aims to answer how regulation affects launch strategies in the on-patent pharmaceutical sector and incorporates covariates for regulation, market, firm and molecule characteristics. This chapter uses substantial IMS price and volume data from 20 markets (South Africa and 19 OECD markets) during 1999-2008. Incorporation of price information provides a more accurate and sensitive control for the outcome of pricing regulations aimed at innovative medicines rather than using dummies to control for regulation. Discrete time implementation of the proportional hazard model with complementary log log regressions are run to account for the monthly grouping of launch times in the IMS database. Results are compared to the continuous time Cox model for the base case. The analysis is carried out for molecules that have launched in at least half of the markets in the database to avoid bias due to locally oriented molecules and increase the generalizability of the results.

Hypotheses tested in Chapter 3 are as follows:

H 3.1: Does the hazard of launch increase in expected new molecule prices?

> It is expected that the higher expected prices, the higher the probability of launch since price controls reduce returns from R&D investments and jeopardize

incentives to entry. In addition, launch in low priced markets results in profit spillovers to subsequent markets that reference it in price setting.

H 3.2: Do firms strategically launch later in price controlled markets and manipulate launch prices?

Firms are global optimizers and have to increasingly consider the ineterdependencies across markets to determine launch strategies. Firms can adopt two startegies to avoid knock-on effects of regulations in subsequent markets. Avoiding launch in small, low-priced markets would block parallel trade from the low-priced market to the high-priced markets and prevent price spillover due to external referencing (or delay these by launching later in the product lifecycle). Alternatively, firms may opt to launch products across markets at converging prices and keep the price knock-on effects to a minimum.

H 3.3: Does market size have a significant effect on hazard of launch controlling for expected price?

Although prior evidence is contradictory, it is expected that a higher expected market size (which is measured at the therapeutic subgroup level rather than at an aggregate level) will increase incentives to entry and result in faster adoption.

H 3.4: Does competition increase the hazard of adoption for new molecules?

Industrial organization considers higher market concentration as a structural barrier to market entry and predicts that high market concentration is associated with lower equilibrium level of entry. Therefore, I expect that market power concentration in therapeutic subgroups to reduce the hazard of launch.

H 3.5: Do firm economies of scale and scope increase the hazard of launch?

It is expected that scale and scope economies result in cost advantages in clinical trials, advertising, registration and price approvals, and learning effects in R&D with knowledge spillovers across different drugs. I expect that the higher global sales of the firm and the number of molecules the firm has launched, the higher is the hazard of launch.

H 3.6: Do therapeutically/commercially important molecules diffuse faster internationally?

The on-patent sector is an oligopolositic market environment with quality-based competition. Therefore, it is expected that therapeutically important molecules (as proxied by the extent of global reach and global sales) obtain faster approval and price mark-ups that increase incentives for faster entry.

Results in Chapter 3 confirm hypotheses H 3.1–3.3. Price regulation and lower market size are significantly associated with reduced delays in adoption of innovative molecules. The price effect is more robust across different specifications compared to the volume effect, which emphasizes the key role of expected price in new molecule launches. Results indicate strategic firm behaviour in terms of late launch (or non-launch) in low-priced markets and convergence in pricing strategies to avoid knock-on effects in foreign markets through external referencing and parallel trade spillovers. Consistent with H 3.4, higher therapeutic subgroup concentration was found to discourage fast adoption. However, an increase in the number of substitute molecules was associated with an increase in the hazard of launch, which suggests that price controls may increase concentration at the therapeutic subgroup level further decreasing the incentives for entry.

Findings confirm H 3.5 and H 3.6; significant firm and molecule heterogeneity is observed in the probability of launch. In particular, pharmaceutical innovations of firms that have prior launch experience in several markets are adopted internationally faster. Firms with more established local experience (higher number of local molecules) and higher sales revenue obtain faster market access, which might be explained by higher ability to overcome barriers to entry. Similarly, consistent with prior findings from the literature, therapeutically more important molecules are adopted more quickly.

Chapter 4

The main research question in Chapter 4 is how regulation affects timing of generic availability relative to the first global generic launch across the main OECD markets during 1999–2008 controlling for market, firm and molecule characteristics. Regulation is mainly captured by the product of lagged average retail branded prices and the median generic-branded price ratio in the destination market, which is a more refined approximation compared to using branded prices only or treatment dummies for price controls. Due to the grouped nature of survival times in the IMS database, the empirical strategy adopts discrete time implementation of the proportional hazard model using

complementary log log regression and proportional odds model using logistic regression. In both cases, parametric and non-parametric duration dependence is used to test the robustness of parameter estimates to different model specifications. The regressions are estimated for generic molecules that launched both in the US and UK to exclude molecules that launched exclusively in one market, and had a first global generic launch during or after 1993.

Hypotheses tested in Chapter 4 are as follows:

H 4.1: Does the hazard of generic adoption increase in expected generic prices?

Higher generic prices (proxied by average branded prices times the generic-branded price ratio in the market) are expected to increase incentives for generic entry. Given that generics compete based on price, the higher the price mark-up of brandeds over generics, the higher the market share that generics can capture. Therefore, generic entry is expected to be faster in markets with high prices and a low generic-branded price ratio (*Pg/Pb*).

H 4.2: How does hazard of generic adoption depend on the expected generic market size?

Generics business model is based on a low-margin price competition. The prospect of capturing a substantial volume, therefore, is expeted to be a key driver of generic entry. Generic market size is controlled by the multiple of two factors: i) branded molecule sales, and ii) average market share captured by generics in individual markets. This approach takes into account local variations in generic penetration rates across countries.

H 4.3: How do ex-ante expectations about generic competition affect hazard of generic adoption?

Higher generic competition drives prices down and reduces the market share captured by individual competitors since generic products are commodity products that cannot be successfully differentiated through promotion efforts. It is, therefore, expected that the higher number of generic competitors in the country and the higher the concentration of generic manufacturers at the therapeutic class level, the lower the hazard rate.

H 4.4: Is generic entry faster for therapeutically more important molecules?

Therapeutic importance of the molecule may affect adoption speed in several ways. First, the originator has a longer adoption delay as therapeutic importance decreases, which reduces the duration of the exclusivity period during which the originator builds brand loyalty, the main strategic advantage of branded products over generic competitors. Second, therapeutically important molecules are usually granted higher price mark-ups due to improved quality attributes, which should increase generic entry based on hypothesis H 4.1.

H 4.5: Do firm economies of scale and scope significantly increase the hazard of launch in the generic sector?

Scale effects are expected to be less important in the generic sector due to lower structural entry barriers associated with R&D and advertising in the branded sector. However, economies of scale may allow vertical integration in the supply chain as well as mergers with other generic manufacturers to decrease costs, which will increase incentives to entry. Economies of scope would allow lower-cost entry as the firm can switch quickly and less costly from one product line to another. Economies of scope due to knowledge spillovers across different product lines may further lower development and entry costs.

Consistent with hypotheses H 4.1 and H 4.2, Chapter 4 finds robust and highly significant positive effect of expected generic prices and expected market size on the hazard of first generic launch. Controlling for branded prices, the closer the generic and branded prices are, the lower is the hazard of launch. Price differentials between generics and branded drugs allow generics to capture a higher share from branded sales (in markets with reference price systems co-payments, defined as a function of the generic-branded price difference, provide incentives for generic use). The significance of expected market size suggests that demand-side measures to promote generic demand should supplement any supply-side oriented measures to sustain the generic market.

Findings in Chapter 4 indicate that competition slows down entry of generics, which is opposite to the impact of competition on the hazard of launch of new molecules. Contrary to the hypothesis H 4.3, the higher the concentration of generic manufacturers in the ATC4 in each country, the higher is the hazard of launch. This could be due to a

higher untapped market opportunity in a commodity market when the concentration is high.

At the firm level, local sales are better predictors of the hazard of launch compared to the global firm sales, which partially contradicts hypothesis H 4.5. Consistent with hypothesis H 4.5, firms' with a higher number of molecules on average have quicker generic launch which suggests economies of scope. The fact that local sales predict launch better could be a reflection of the fact that generic manufacturers tended to be largely regional players in the past. However, global companies are increasingly emerging in the generics business (e.g. Teva and Ranbaxy), in particular low-cost producers from Eastern Europe, China and India are impacting margings on a global scale driving acquisitions to build scale to offset such margin pressure (Jorge 2009).

The final chapter, Chapter 5, wraps up the thesis by reviewing the empirical chapters and ties up the hypotheses; presents the results with policy implications and highlights the contributions to the literature as well as the limitations in the empirical analyses. Finally, suggestions on possible extensions of the analyses carried out in the thesis are provided as a direction for future research.

CHAPTER 2

2 Trends in the Adoption of Pharmaceutical Innovation and Generic Competition as a Response to Regulatory Changes during 1960-2008

2.1 INTRODUCTION

How regulation affects adoption of innovation is a question open to empirical scrutiny, especially in highly regulated industries such as the pharmaceutical industry where products are protected by Intellectual Property Rights (IPR). The existing evidence in the pharmaceutical context is very limited despite the fact that several studies have been carried out. Particularly important is the role of the timing of drug launch, which is typically carried out by international companies following some corporate strategy. Paradoxically, the impact of regulation on generic products within a therapeutic group has received even less attention. Expected proliferation of bioequivalent products in the near future, rising concerns over cost containment and the resulting push for genericization makes timing of generic launch a question of interest both for the pharmaceutical industry and the policy makers. The purpose of this chapter is to investigate how policy changes related to the regulatory environment impinge on the adoption of pharmaceutical innovation (new molecules) and imitation (generic products) across the main OECD markets over the period 1960-2008. Comprehensive IMS data is used to analyze cross-national adoption of 845 molecules from 14 different anatomic therapeutic categories by survival analysis methods.

Regulation of market access and prescribing was historically introduced to ensure product efficacy and safety following the Thalidomide tragedy in 1960s. Regulation throughout the history has aimed to balance the opposing interests of the industry through patents and those of the consumers through regulation of market access and price controls. Patents generate the financial incentives to innovate by providing market exclusivity. Product efficacy and safety are critical to the health of consumers but are not immediately observable. Drug regulations, therefore, aim to keep unsafe and ineffective drugs off the market to protect consumers, at the price of diminishing incentives to innovate. As descried in Chapter 1, post-launch regulations are aimed at correcting the failures in the pharmaceutical sector, of which monopolistic power granted by patents and price insensitivity due to third party payment are the most

prominent ones. Sections 2.3.1 and 2.3.2 provide additional background on the historical development of pharmaceutical regulation. This chapter aims to assess trends in the adoption delays of pharmaceutical technologies as a response to policy changes in pharmaceutical regulation.

Firms facing a competitive environment would ideally launch new chemical entities (NCE) as quickly as possible into several markets to amortize the substantial R&D outlays. However, at least two regulatory hurdles have to be overcome before commercializing a new drug product. The first hurdle is that manufacturers have to prove the threefold requirement of quality, safety and efficacy of new molecules which is estimated to take around ten years of pre-clinical and clinical research (Permanand 2006). The second hurdle typically includes the review of the new product dossier by the regulatory authority (FDA[9], EMEA[10] or any national authority) and approval of marketing authorization (MA). Finally, the third hurdle following marketing approval is pricing and reimbursement (P&R) which involves negotiations between manufacturers and P&R authorities regarding the price of the new product and its reimbursement status. This latter hurdle, namely price regulation, can arguably delay launch through the negotiation processes alongside the resulting firm strategies of delaying or foregoing launch in low-priced markets[11] (Danzon, Wang et al. 2005; Kyle 2007). Non-homogeneity in these hurdles across markets results in launch delays, with welfare implications for the consumer and the pharmaceutical producer[12].

The importance of innovation lies in that lags in the adoption of new pharmaceutical innovations may affect consumer welfare through impaired spatial equity and access to new drug products, in particular cost-effective products. Empirical evidence shows that lack of access to new drugs leads to compromises in health outcomes (Schoffski 2002), shifts volume to older molecules of lower therapeutic value (Danzon and Ketcham 2004) and results in higher expenditures on other forms of medical care and

[9] Food and Drug Administration

[10] European Medicines Agency had the acronym of EMEA until December 2009, as of December 2009 the acronym is EMA. I keep the old acronym to be consistent with the literature until 2010

[11] The US, UK and Germany do not require price approval; however, in the UK, Germany and several other markets cost-effectiveness evaluation may further delay the adoption of new pharmaceutical innovation as the fourth hurdle

[12] According to the Sector Inquiry by the European Commission (2009), pharmaceutical companies may submit a pricing and reimbursement dossier before the marketing authorisation is officially granted in France, Italy, Netherlands and Sweden whereas in most other Member States, a submission for pricing and/or reimbursement can only be made after the marketing authorisation has been granted (DG Competition 2009).

compromises in quality of health care (Kessler 2004; Wertheimer and Santella 2004). Innovative medications offer economic benefits through fewer work days missed and lives saved (Lichtenberg 1996; Lichtenberg 2003a; Hassett 2004; Lichtenberg 2005). Delays in the launch of new molecules could be costly to the pharmaceutical industry through reduced market exclusivity periods, lower returns to R&D and eventually fewer innovations[13].

New molecules face an additional source of competition, namely generic competition within a therapeutic group, once the product goes off patent. Generic products are by definition bioequivalent, and therefore perfect substitutes (on objective quality grounds) to the branded versions that usually claim substantial price mark-ups over the marginal cost of production[14]. Generic entry enhances efficiency and competition in the drug market; however, the main hurdle before generic entry is the cost of bioequivalence tests which are significantly cheaper than the average costs of safety and clinical evaluation[15]. Generic imitations largely freeride on the R&D efforts of originator firms, which enables them to compete solely based on price. Timely adoption of generic products, therefore, carries significant importance to improve allocative efficiency and stimulate competition (DG Competition 2009).

The analysis in this chapter draws upon an extensive database on the timing and entry of new pharmaceutical molecules (innovation effects of market regulation) along with the entry of bioequivalent competitors (competition effects). The main contribution of this chapter lies in the following. First, this is the first study to analyze historical trends using an extensive database in contrast to prior studies that restrict the analysis a specific, narrow time-period. Second, I examine the adoption of both new on-patent active ingredients and older active ingredteints that face generic competition. Although the trade-off between innovation and cost cutting competition is one of the most important features of pharmaceutical market dynamics, the joint consideration of these technologies has been traditionally left out of the analysis of drugs adoption. Finally, the analytical framework in this chapter is based on two main regulatory changes that

[13] Vernon (2005) shows that both profit expectations and lagged cash flows have significantly positive impacts on pharmaceutical firms' R&D investment intensity (Vernon 2005)

[14] A generic is defined by the European Directive 2004/27/EC as "a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies."

[15] 18 times cheaper according to the Pharmaceutical Manufacturers Association (Pharmaceutical Manufacturers Association 1993)

reshaped the barriers to entry substantially: 1) the US Hatch-Waxman Act in 1984[16]; 2) the establishment of the European Medicines Agency (EMEA, currently abbreviated as EMA) in 1995 and the adoption of the centralized procedure that grants a Community marketing authorization. This framework defines three sub-periods for the analysis of launch lags, namely, 1960-1984, 1984-1995 and 1995-2008.

The Hatch-Waxman Act, one of the most significant acts in the U.S. healthcare system, was designed to promote generics while improving financial incentives for research and development. The Act allowed generics to win FDA marketing approval by submitting bioequivalence studies, as opposed to clinical data that are costlier to compile. It also granted a period of additional marketing exclusivity to patent protected drugs to make up for the time lost in drug development in the research-based pharmaceutical industry (Mossinghoff 1999).

The European Medicines Agency was established in 1995 to create a single European market for pharmaceuticals. EMEA highlights a key regulatory development for the European pharmaceutical market within the last two decades. The Agency is responsible for the scientific evaluation of applications for European marketing authorisation for medicinal products, centralised procedure that grants a centralised marketing authorisation valid in all European Union (EU) and EEA-EFTA states (Iceland, Liechtenstein and Norway). In addition, the EMEA monitors the safety of medicines and takes appropriate actions in cases of adverse drug reactions that change the benefit-risk balance of a medicinal product.

This chapter posits that adoption of pharmaceutical technologies responds to regulatory changes. The main hypothesis is that the Hatch-Watchman Act (1984) speeded up adoption of new molecules due to the reduction in legal barriers to entry through the provision of additional monopoly period for innovative medicines (patent term restoration) and the reduction in transaction costs for generics through Bolar provisions. My second hypothesis is that the EMEA has reduced legal costs by harmonizing the approval procedures across the EU and speeded adoption of centrally approved new pharmaceutical innovations. I used 1995 as the cut-off date due to its significance in the creation of a single market in the EU although the Directive 2004/27/EC in 2004 marks

[16] Coppinger, Peck et al. (1989) used the same-cut off value and suggested 1984 as a pivotal year in the history of drug introduction patterns between the US and the UK (Coppinger, Peck et al. 1989)

another important regulatory change by the adoption of new rules on pharmaceutical data exclusivity and the European Bolar provision clause.

This chapter compares the evolution of the adoption timing over time and across markets using 1984 and 1995 as cut-off points to define Kaplan-Meier estimates of median delays. The impact of the EMEA centralized procedure is analyzed by comparing median delays pre- and post-1995. Median delays in adoption are preferred over mean delays due to the skewed nature of the survival time data. The changes in median delays are investigated by using Cox proportional hazard model and a difference-in-difference (DiD) analysis to investigate whether the Hatch-Waxman Act and the creation of the EMEA had a statistically significant impact on the adoption of pharmaceutical technologies over time.

The organisation of the chapter is as follows. Section 2 describes the data and methods used in the analysis; Section 3 presents the results of the analysis with respect to periods defined by the policy changes in 1984 and 1995 in the US and EU respectively; and finally Section 4 concludes.

2.2 DATA AND METHODS

2.2.1 Data

The IMS data used in the analysis contains quarterly sales in dollars and standard units for molecules from 14 different ATC groups and 20 countries[17],[18]. Remaining data fields include global and local launch dates of drug products, pharmaceutical form, anatomic therapeutic class of the product, the distribution channel of sales (hospital vs. retail), and patent protection status of the drug. The markets in the data set, all based in the OECD except for South Africa, comprise the majority of the global pharmaceutical market. In this chapter, I report the results for the seven big pharmaceutical markets comprised of the US, Japan and the EU5 (the UK, Germany, France, Italy, and Spain).

Multi-country drug lag studies that analyze the time differentials in adoption of drugs across multiple countries apply several criteria to identify significant new chemical

[17] IMS (Intercontinental Medical Services) MIDAS data was collected at Merck Sharp and Dome Limited (MSD) premises in Hoddesdon, UK.

[18] Australia (ALIA), Austria (AUS), Belgium (BEL), Canada (CAN), Finland (FIN), France (FRA), Germany (GER), Greece (GRE), Italy (ITA), Japan (JAP), Netherlands (NET), Poland (POL), Portugal (POR), South Africa (SAF), Spain (SPA), Sweden (SWE), Switzerland (SWI), Turkey (TUR), the UK, and the US

entities (NCEs). The choice of molecules is important because some molecules are exclusively launched in one geographic market; the inclusion of these molecules would introduce a bias in a multi-country survival analysis. Therefore, the analysis excludes one-market molecules which are either therapeutically or commercially of limited importance. In the IMS database, 969 molecules launched exclusively in one market (21% of all molecules) (see Table B.1 for the distribution of the number of markets in which molecules launched). As a minimum requirement of potential global importance, following the approach of Parker (1984) and Danzon (2005), this chapter considers molecules that have launched in both the US and the UK as an indication of therapeutic significance and potential for global launch. Several studies find a direct relationship between the therapeutic contribution of a new drug and its likelihood of achieving widespread introduction (Parker 1984; Barral 1985). This finding suggests that most one-market new chemical entities (NCEs) do not simply disperse among countries more slowly than others but that they are never going to be widely available due to their marginal therapeutic advantages. Including molecules that launched in the US and the UK, therefore, avoids potential bias. Hereafter, this potentially global set of molecules is referred as "US&UK molecules".

Table 2.1 Number of Molecules by Period of Global Launch

Period	*US&UK (All)*	*US&UK (Generic)*
[1960-1984)	385	214
[1984-1995]	194	90
[1995-2008]	266	46
TOTAL	845	350

In addition, I define a global molecule set comprised of molecules that diffused to all twenty markets in the database. These two sets provide a means to compare relative drug lags for molecules with different levels of international spread and to assess whether there exists a systematic difference between the two. For brevity, I report only the results for US&UK molecules only. Findings for global molecules are broadly in line with the estimates for US&UK molecules. Table 2.1 presents the breakdown of molecules by the period of global launch (see Table B.2 for the breakdown of molecules by country). The majority of the molecules had their global launch during 1960-1984. In total, 845 molecules were launched in the US and UK since 1960. Less than one-fourth of these molecules diffused to all markets. Only 350 of the molecules had a generic

launch both in the US and UK. The US, UK, Germany, France, Canada and Switzerland are among countries that had the greatest number of launches whereas Portugal, Japan, Spain, Belgium, Sweden and Turkey had the least number of launches. The highest number of generic molecule launches occurred in the US, UK, Germany, Canada, Poland, Australia and Netherlands.

2.2.2 Methods

The methodology in this chapter relies on survival analysis to estimate the median delays, semi-parametric survival and difference-in-differences analysis to assess the impact of regulatory policies such as the Hatch-Waxman Act (1984) and the EMEA (1995) on the speed of pharmaceutical technology adoption. Survival analysis is a methodology used to analyze time-to-event data (also known as survival time data, duration data, or transition data). The main shortcoming of commonly used models for empirical analysis, such as the ordinary least square (OLS) estimation, is the assumption of normally distributed errors conditional on the regressors. A key distinguishing characteristic of survival data is that survival data are usually censored and have non-normal, non-symmetric (skewed) distributions. Duration analysis is the appropriate methodology to analyze such data as it can accommodate censoring and it does not assume normality as the OLS model does. Censoring occurs when the exact failure time is unknown. In the context of this chapter, molecules that have not been adopted locally in a particular market by the end of Q3 2008 are right-censored[19]. In such cases, the exact failure date is unknown; it is known only that the failure time is greater than the time spent under risk following global launch. Survival analysis methods used in this chapter assume that the process that gives rise to censoring of survival (adoption) times is independent of the survival time process.

First, I use non-parametric Kaplan-Meier estimates to characterize the nature of lags and analyze patterns across markets and over time. The advantage of the nonparametric approach is that it provides a reasonably good fit for any distribution without any prior assumptions about the functional form of failure times. The analysis takes place at the molecule level, whereby I define subjects to be molecule-country pairs. The failure event is therefore the launch of a given molecule in a particular market. The failure

[19] For truly global molecules right-censoring is not an issue since the exact launch time of every molecule is known in all countries.

indicator is set to one if the molecule launches in the given market and to zero if the molecule is censored (i.e. does not launch by the end of the observation period 2008). The time to failure event is equal to the time lapse from the first global launch date of the molecule (the onset of risk) to the date of launch in a particular country (the failure) [20]. The global launch date is the first date the molecule launched in any country in the IMS database. The local launch date of each molecule is defined as the minimum launch date of drug products with the same active ingredient; this takes account of the fact that drug products with the same active ingredient (molecule) may differ across markets with respect to the launching corporation, dosage, and form.

Missing global launch dates are proxied by the minimum local launch date across all twenty markets. The rationale for this approximation is that global molecules are most likely to launch first in any of the 20 countries in the dataset. The first known global launch for global molecules in the dataset occurred in one of the 20 markets for 90% of the global molecules that launched after 1995. Therefore, the potential bias introduced due to this approximation is minimal.

In the case of generic adoption, risk onset is defined as the launch date of the first generic copy of a given active ingredient across the twenty markets. Based on this risk defintion, this approach analyzes differentials in generic availability across the countries in the dataset. An alternative definition for risk onset could be local protection expiry dates, which would enable quantifying delays in generic entry post-patent expiry. However, I did not follow this approach as expiry dates are not available for the majority of the products. Some molecules never had patent protection and were launched as generics (e.g. acyclovir). In 56% of cases expiry date of a molecule exceeds local launch of the first generic by more than a year, which could be due to the presence of copy products in some markets, or launch of pseudogenerics[21] (also known as authorized generics). Instead, as in the case for new molecules, I estimate relative adoption delays in generic competition with respect to the first global generic launch.

Similarly, differential timing of launch could be due to variations in market authorization dates or delays in pricing and reimbursement procedures as well as

[20] Spain, Turkey, Belgium, Greece, Portugal, Spain, South Africa have only retail channel data; therefore, the first local launches in these countries represents launch in the retail sector.

[21] Pseudogenerics are generics marketed by brand-name companies to compete against independent generics

strategic firm delays to avoid threats of price spillovers across markets (Danzon, Wang et al. 2005). Unavailability of data precludes isolating delays due to these components.

2.2.2.1 Non-parametric Kaplan-Meier Estimates

The survivor function estimate $\hat{S}(t)$, the probability that the subject fails beyond time t, is given by (Kaplan and Meier 1958):

$$\hat{S}(t) = \Pr(T > t) = \prod_{j|t_j \le t} (1 - \hat{p}_j) = \prod_{j|t_j \le t} \left(\frac{n_j - d_j}{n_j} \right)$$

where $p_j = \Pr\left(t_{j-1} < T \le t_j \mid t_{j-1} < T\right)$ is the conditional probability that the subject fails within the interval $\left[t_{j-1}, t_j\right)$. n_j is the number of subjects at risk, d_j is the number of failures at time t_j and $t_1, t_2, \ldots t_k$ are the observed failure times. The estimate of the survival function is given as the product of conditional survival probabilities over all observed failure times (i.e., country-molecule launches) less than or equal to time t.

Kaplan-Meier estimates of the survivor function *S(t)* at time *t* are obtained using Stata 10. The median survival time corresponds to the smallest time point at which the survivor function is less than or equal to 0.5 ($\hat{S}(t) = 0.5$), i.e. the time point at which half of the molecule candidates have launched. Mean survival time, on the other hand, is estimated as the area under the survival curve[22]. As mentioned before, I mainly use median delays to draw inferences due to the significantly right-skewed nature of failure time distributions (see Figure B.1 in Appendix B). Additional technical details on non-parametric estimation are provided in Appendix B.2.

The median survival times in each market are estimated by period of molecule entry into the risk set, i.e. first global launch during 1960-1984, 1984-1995 and 1995-2008. The cut-off points 1984 and 1995 were chosen as the two major regulatory changes with potential effects on the timing of adoption in the US and Europe respectively. The objective of the empirical analysis in this chapter is to provide evidence on the behaviour of failure (adoption) times of new molecules and generic competition across

[22] The command *rmean* in Stata calculates mean survival time restricted to longest follow-up time. The command *emean* calculates the mean survival time by exponentially extending the survival curve to zero

the OECD before and after these two landmark changes in the regulatory environment. With this framework, the evolution of relative launch lags can be compared both across countries and over time.

2.2.2.2 Semi-Parametric Cox Proportional Hazard Model Estimation

Cox proportional hazard (PH) model was used to estimate the impact of the first launch period on the hazard of adoption. The hazard rate for the *j*'th subject in a Cox model is specified as:

$$h\left(t;\mathbf{z}_j\right)=h_0\left(t\right)\exp\left(\mathbf{z}_j\boldsymbol{\beta}_x\right).$$

The baseline hazard $h_0(t)$ is not parameterized and is left unestimated but the effects of the covariates $\mathbf{z}_j=\left(z_{1j},z_{2j},...,z_{pj}\right)$ are parameterized. As no assumption is made about the shape of the hazard over time, the Cox model provides significant flexibility in analysis. The parameter β_k describes the change in the hazard on a logarithmic scale for a change in the corresponding covariate z_k of 1 unit, while all other covariates are kept fixed. Positive parameter estimates ($\hat{\beta}_k>0$ equivalently $\exp\left(\hat{\beta}_k\right)>1$) are associated with an increased hazard rate. The Cox PH model provides no estimate of the intercept as it is subsumed into the baseline hazard. The Cox model estimates parameters using partial maximum likelihood that works with likelihood contributions at each failure times, i.e. the conditional probabilities of observing the actual subject experiencing a failure given that there was a failure at that time instant (see Appendix B.3 for details).

2.2.2.3 Difference-in-Differences Analysis for Policy Analysis

The economics literature has made wide use of difference-in-differences (DiD) analysis to analyze the impact of policy interventions by treating the policy changes as quasi-experimens. This approach makes use of the conceptual framework and terminology of "randomized experiments". Quasi-experiments differ from randomized experiments in the lack of randomness in the assignment of subjects to treatment and control groups; quasi-experiments are known as natural experiments if nature has assigned subjects to groups. Due to lack of randomization, there can be systematic differences between the treatment and control groups in quasi-experiments (Meyer 1995).

The data structure that the DiD approach uses for policy analysis is pooled cross-section data over time. During each time period a new random sample is taken from the population. This is different from a panel data structure in that panel data is based on replicability; the same subject is followed over time. Observations across different time periods in a pooled cross-section data are independent, but not necesarrily identically distributed. Period dummies are included in the analysis to account for the aggregate changes over time. Interaction of period dummies with explanatory variables allows partial effects to change over time for policy analysis using natural experiments.

In the simplest case, data is available for two time periods (before and after the treatment) and two groups: i) a treatment group where the policy is applied, and ii) a control group that does not receive the treatment but is affected by other factors that affect the treatment group. The impact of the treatment on the outcome variable is assessed by interacing the treatment variable with the time period dummy. The underlying model to assess the impact of a policy change assumes the following form (Wooldridge 2002)

$$y = \alpha + \delta_0 \cdot d_{post} + \beta \cdot d_T + \delta_1 \cdot d_{post} \cdot d_T + \varepsilon,$$

where y is the outcome variable of interest and T indicates the treatment group. d_T is the treatment dummy that equals unity for subjects in the treatment group and zero otherwise; d_T captures possible differences in the treatment and control group before the policy change. The dummy variable d_{post} equals unity for the period following the policy change and zero before the policy is implemented; it captures aggregate factors that affect y over time in the same way for both groups. δ_1 is the coefficient of the interaction term which equals unity for observations in the treatment group after the policy change. The OLS estimator of δ_1 is known as the difference-in-differences estimator. Assuming $E[\varepsilon \mid d_{post}, d_T] = 0$:

$$\bar{y}_{T,post} = E[y \mid d_{post} = 1, d_T = 1] = \alpha + \delta_0 + \beta + \delta_1$$

$$\bar{y}_{T,pre} = E[y \mid d_{post} = 0, d_T = 1] = \alpha + \beta$$

$$\bar{y}_{C,post} = E[y \mid d_{post} = 1, d_T = 0] = \alpha + \delta_0$$

$$\bar{y}_{C,pre} = E[y \mid d_{post} = 0, d_T = 0] = \alpha .$$

Using the above equations, $\hat{\delta}_1$ can be expressed as:

$$\hat{\delta}_1 = (\bar{y}_{T,post} - \bar{y}_{T,pre}) - (\bar{y}_{C,post} - \bar{y}_{C,pre}),$$

where T and C are the treatment and control group; *pre* and *post* indicate the period before and after the policy change respectively.

$\hat{\delta}_1$ considers the expected change in the outcome variable in the treatment group $(\bar{y}_{T,post} - \bar{y}_{T,pre})$ but given that factors other than the policy change can affect the change in the mean response $(\bar{y}_{C,post} - \bar{y}_{C,pre})$ is deducted to account for changes in the mean response that would have occurred without the policy interventions; this allows for both group-specific and time-specific effects. The DiD estimator is unbiased if the policy change is not systematically related to other factors that affect the outcome.

I use the difference-in-difference estimator to explore the impact of the US policy change in 1984 (the Hatch Waxman Act) and the impact of the EU policy change in 1995 (the creation of the EMEA). To analyze the impact of the 1984 Act on the adoption speed in the US, I estimate the following model:

$$y = \alpha + \delta_0 \cdot d_{1984} + \beta \cdot d_{US} + \delta_1 \cdot d_{1984} \cdot d_{US} + \gamma d_{country} + \varepsilon,$$

where d_{US} is a dummy equal to unity if the destination market is US and d_{1984} is the period dummy equal to 1 for local launches after 1984. $d_{country}$ is a vector of country dummies excluding the reference country and the US. y is the failure time of country-molecule pairs. The outcome variable y is specified as both failure time (in years) and log of failure time (log years) due to the skewed nature of the survival time data, expecting the log transformation to provide a better fit to the regression model. The estimate $\hat{\delta}_1$ is preferable over the simple difference estimator $(\bar{y}_{US,post84} - \bar{y}_{US,pre84})$ because reasons unrelated to the policy change could affect the mean response over time. For instance, internationalization of pharmaceutical corporations and harmonization in MA regulations across countries could explain some of the reduction in differential delays in adoption.

Analogously, the impact of the EMEA on the adoption of pharmaceutical technologies in the EU is estimated by the following model[23]:

$$y = \alpha + \delta_0 \cdot d_{1995} + \beta \cdot d_{EU} + \delta_1 \cdot d_{1995} \cdot d_{EU} + \gamma d_{country} + \varepsilon,$$

where d_{EU} is a dummy variable equal to unity of the destination market is the EU[24] and d_{1995} is the period dummy equal to 1 for local launches after 1995. $d_{country}$ is the set of country dummies excluding the reference country Australia.

2.3 RESULTS

2.3.1 Trends in the Adoption of Pharmaceutical Innovation

Evolution of Median Delays over Decades

Figure 2.1 shows the overall Kaplan-Meier survival estimates $\hat{S}(t)$, i.e. the probability that molecules are adopted after time *t*, for molecules that first launched globally during 1960-1984, 1984-1995 and 1995-2008 respectively. The higher the curve is, the higher the area under the curve, and therefore, the higher the mean and median survival times are.

The overall global trend in median (and mean) survival times for US&UK molecules across the twenty markets from 1960 to 2008 is decreasing. This implies that relative delays in the adoption of new pharmaceutical technologies have decreased over the decades. While the overall median is 11 years for molecules with a global launch in 1960-1985, the median drops to 4 and 2 years for molecules that launched in 1984-1995 and 1995-2008 respectively (see Table B.3 in Appendix B for median delays in individual countries for each period). Log rank test for the equality of the survival

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[23] With additional covariates in the regression equation, the interpretation of δ_1 remains unchanged, although the representation is no longer given by $\hat{\delta}_1 = (\bar{y}_{T,post} - \bar{y}_{T,pre}) - (\bar{y}_{C,post} - \bar{y}_{C,pre})$

[24] EU countries were comprised of Austria, Belgium, France, Finland, Germany, Greece, Italy, Netherlands, Portugal, Spain, Sweden and the UK. Poland was excluded from the regressions since it joined the EU only in 2004

curves rejected the null hypothesis of equal survival behaviour for the three periods ($p<0.0000$)[25].

Figure 2.1 Overall median delays with respect to period of global launch

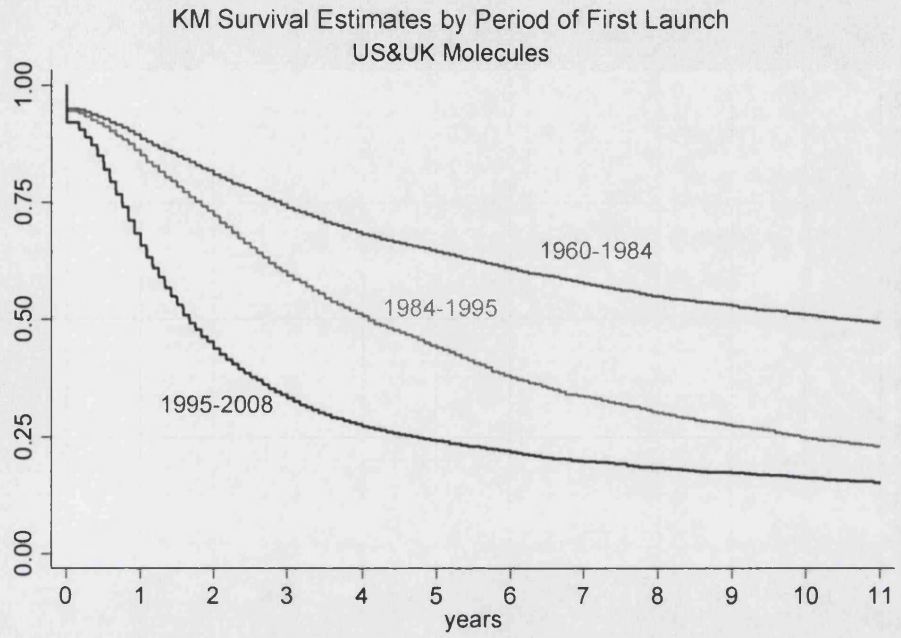

Table 2.2 Median delays and confidence intervals by period of first launch

Period	*Subjects*	*Median*	*Std. Err.*	*[95% Conf. Interval]*	
1960-1984	7186	10.59	0.33	9.92	11.25
1984-1995	3726	4.08	0.11	3.92	4.33
1995-2008	5125	1.67	0.04	1.59	1.75

Non-overlapping confidence intervals for median adoption delays of new molecules in Table 2.2 suggest that difference in medians is significant. Next, I incorporate potential country effects on median adoption times and estimate a semi-parametric Cox proportional hazard model to assess the significance of the first launch period.

Cox Proportional Hazard Model: Test of Survival Trend Significance

Cox proportional hazard (PH) models were estimated to test for the significance of the first launch period. The Cox model allows incorporating factors that may have an influence on the adoption times. Considering the fact that country of destination may

[25] Equality of survival curves rejected even after stratifying by country

have an effect on the adoption speed of molecules and result in possible intra-group correlation, I estimated both fixed effects and random effects Cox PH models.

The fixed effects specification assumes countries have a direct multiplicative effect on the hazard function. In other words, molecules in all countries have the same baseline hazard. The effect of a country multiples the baseline hazard function up or down depending on the sign of the estimated coefficients. A direct fixed-group effect is modelled by including country-specific indicator variables for each country except one[26]. The hazard function for molecule j and country k pair is assumed to be $h_{jk}(t) = h_0(t)\exp(x_{jk}\beta + \delta_k)$, where δ_k is the fixed effect for country k. The independent variables x are period dummies that indicate whether the first global launch of molecule j occurred in the given period[27].

In the random effects specification, the effect of a country is assumed to be random and have a multiplicative effect on the hazard function (known as *Shared Frailty Model* or *Random Effects Cox Model*)[28]. For molecule j and country k, the hazard is $h_{jk}(t) = h_0(t)\alpha_k \exp(x_{jk}\beta)$, where α_k is the country-level frailty. Frailties are unobservable positive quantities assumed to have mean 1 and variance θ that is estimated from the data. When $\theta = 0$, the Cox shared-frailty model reduces to the standard Cox model. Assuming $\nu_k = \ln \alpha_k$ for the random term, the hazard can be rewritten as $h_{jk}(t) = h_0(t)\exp(x_{jk}\beta + \nu_k)$. As in the fixed effects specification, I assume the independent variables x are period dummies that indicate whether first global launch of the molecule occurred in the given period[29].

Estimates of the fixed-effects and random-effects Cox model are presented in

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[26] Alternatively, country effects can be accounted for by stratifying on hospital with the *strata()* command in STATA. In this case, the baseline hazard is allowed to be different for each country rather than constraining them to be multiplicative versions of each other

[27] The command used to estimate fixed effects is

eststo fixed: xi: stcox Global_Launch_in_60-84 Global_Launch_in_95-08 i.country,

where the first two variables are dummy variables that indicate whether the molecule launched globally during 1960-1984 and 1995-2008 respectively.

[28] A frailty is a latent random effect that enters multiplicatively on the hazard function.

[29] The STATA command used to estimated the Random Effects Cox model is

eststo random: stcox Global_Launch_in_60-84 Global_Launch_in_95-08, shared(country)

Table 2.3 and Table 2.4. Both the fixed effects and the random effects indicate that hazard of launch[30] is significantly higher for molecules that first launched during 1995-2008 compared to 1984-1995. Similarly, the hazard is higher for molecules that launched in 1984-1995 compared to 1960-1984. Given that the estimated frailty variance $\hat{\theta}$ is 0.16 and the significance level of the likelihood-ratio test of $H_0 : \theta = 0$, under the random effects model there is significant within-country correlation[31].

The Hausman Test is a generally accepted test for choosing between fixed and random effects. This test checks a more efficient model (random effects) against a less efficient but consistent model (fixed effects) to make sure that the random effects model also gives consistent results, i.e. the null hypothesis that the coefficients estimated by the efficient random effects estimator are the same as the ones estimated by the consistent fixed effects estimator. If the coefficients are the same (insignificant p-value, p-value larger than 0.05) random effects can be used. If the p-value is significant, however, fixed effects are preferred.

The Hausman test used to compare the fixed and random effects specifications indicates that the fixed effects model is the correct specification (p-value: 0.0135)[32]. Based on the fixed effects specification, launch in 1960-1984 decreases the hazard of adoption by 48% and launch in 1995-2008 increases the hazard by 82%, both compared to first global launch in 1984-1995. This implies that the trend for decreasing relative delays for new molecules in Figure 2.1 across decades is statistically significant.

The acceleration of the international diffusion of pharmaceutical products may be attributed to the evolution in barriers to entry as a result of changes in the regulatory environment and an increasingly global and interdependent market environment. The increasing international reach of pharmaceutical corporations as evidenced by the spread of the manufacturing, marketing and innovative R&D activities to different countries has overcome prior geographical barriers. Harmonization of safety and efficacy and marketing authorization requirements across markets has contributed to a reduction in regulatory costs (Busfield 2003).

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[30] The instantaneous probability of launch conditional on not launching before

[31] Discussion of results draws on Section 9.4 in (Cleves, Gould et al. 2008). The interpretation of the hazards in this case is conditional on the frailty.

[32] STATA command: *hausman fixed random*

Table 2.3 Cox regression with country fixed effects: US&UK molecules

Variables	*Hazard Ratio*	*Std Err*	*z*	*P>|z|*	*[95% Conf. Int.]*	
Global launch in 60-84	0.52	0.012	-27.76	0.000	0.497	0.545
Global launch in 95-08	1.826	0.044	24.76	0.000	1.741	1.915
Australia	1.187	0.065	3.11	0.002	1.065	1.322
Austria	0.782	0.045	-4.27	0.000	0.699	0.876
Belgium	1.206	0.065	3.46	0.001	1.084	1.34
Canada	1.035	0.057	0.63	0.530	0.929	1.154
Finland	1.178	0.064	3	0.003	1.058	1.311
France	1.822	0.097	11.26	0.000	1.641	2.023
Germany	0.852	0.047	-2.87	0.004	0.764	0.95
Greece	1.17	0.064	2.89	0.004	1.052	1.302
Italy	0.567	0.034	-9.58	0.000	0.505	0.637
Japan	1.177	0.067	2.88	0.004	1.053	1.315
Poland	0.743	0.041	-5.37	0.000	0.666	0.828
Portugal	0.478	0.03	-11.93	0.000	0.423	0.539
South Africa	0.788	0.046	-4.12	0.000	0.704	0.883
Spain	0.733	0.042	-5.36	0.000	0.655	0.821
Sweden	0.837	0.048	-3.07	0.002	0.747	0.938
Switzerland	1.368	0.074	5.76	0.000	1.23	1.522
Turkey	0.659	0.037	-7.34	0.000	0.59	0.737
UK	2.218	0.116	15.28	0.000	2.003	2.457
US	2.153	0.112	14.73	0.000	1.944	2.384

Table 2.4 Cox regression with country shared frailties: US&UK molecules

Variables	*Hazard Ratio*	*Std Err*	*z*	*P>|z|*	*[95% Conf. Interval]*	
Global launch in 60-84	0.521	0.012	-27.74	0.0000	0.497	0.545
Global launch in 95-08	1.824	0.044	24.72	0.0000	1.739	1.913
theta	0.160	0.050				

Likelihood-ratio test of theta=0: chibar2(01) = 1839.22 Prob>=chibar2 = 0.000
Note: standard errors of hazard ratios are conditional on theta

The following sections present the Difference-in-Difference (DiD) analysis and survival estimates for individual markets in the biggest seven pharmaceutical markets. Next, regulatory changes that could potentially explain the evolutionary trend in the drug lags are explained in more detail.

Difference-in-Differences Analysis for Pharmaceutical Innovation

Table 2.5 presents the results of the DiD analysis that assesses the impact of the US 1984 Act on the adoption of new molecules in the US. The response variable y is the relative delay following the first global launch of new molecules. The treatment group is comprised of molecule-country pairs for which the destination market is the US, and the control group is comprised of molecule-country pairs with a destination in the non-US markets. The policy variable *d_1984* is unity for launches that occur after 1984, and zero if launch is during 1984 or before. The DiD estimator, *US_d_1984*, is significantly negative, which indicates that following the enactment of the 1984 Act has decreased the relative delays in new molecule adoption in the US. Due to the skewed nature of failure times, log of the failure time as the outcome variable results in a better fit. The validity of the DiD estimator is based on the assumption that the underlying trends in the outcome variable is the same for both treatment and control groups. I incorporate country dummies into the specification to control for country effects that could explain some of the variation in the mean delays. DiD results should be interpreted with caution, considering the fact that the US and non-US markets might have been subject to non-common policy changes that affect adoption differentially in these markets.

Table 2.5 DiD Analysis for 1984 US Hatch Waxman Act (New Molecules)

Variables	*y=ln(t)*	*y=t*
US	-0.191 [0.18]	1.061* [0.52]
d_1984	0.800*** [0.05]	6.611*** [0.15]
US_d_1984	-2.737*** [0.24]	-7.085*** [0.51]
Country Effects	Yes	Yes
Number of Observations	16001	16001
Log Likelihood	-35037.94	-62511.5
p-value	0.00	0.00
Akaike Info Criteria	70119.89	125066.9
Bayesian Info Criteria	70288.85	125235.9

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

Table 2.6 presents the results of the DiD analysis for the impact of the EMEA on new molecules. The outcome variable is the log of relative delays (yrs) in adoption. The treatment group is comprised of molecule-country pairs for which the destination market is the EU (Poland is excluded from the analysis because it joined the EU in 2004) and the control group is comprised of subjects with a destination in the non-EU markets. The policy variable *d_1995* is unity for local launches that occur after 1995, and zero otherwise. The DiD estimator, *EU_d_1995*, is negative but not significant in the first specification that includes the US in the set of non-EU markets. When the US is excluded from the analysis the DiD estimator becomes significant. This suggests that differences between the US and EU are not limited to the policy change in 1995. However, a negative estimate for the DiD estimator, *EU_d_1995*, suggests that the establishment of the EMEA has speeded up adoption of new molecules in the EU.

Table 2.6 DiD Analysis for the Impact of EMEA in EU (New Molecules)

y=ln(t)	*DID*	*DID (excluding US)*
EU	-0.992*** [0.11]	-0.843*** [0.11]
d_1995	-0.859*** [0.06]	-0.479*** [0.05]
EU_d_1995	-0.031 [0.08]	-0.411*** [0.07]
Country Effects	Yes	Yes
Number of Observations	15213	14374
Log Likelihood	-33528	-30960.98
p-value	0.000	0.000
Akaike Info Criteria	67098.03	61961.95
Bayesian Info Criteria	67258.26	62113.42

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

2.3.1.1 1960-1984: Stringency in MA Regulations and the US drug lag

The Thalidomide tragedy in the late 1950s, which caused congenital anomalies in babies and a degenerative nerve disorder in pregnant women, marked the beginning of a new era in modern medicine regulation. Until the early 1960s most countries except the Nordic countries and the US had no independent safety and efficacy protocols for new drugs. The US had a regulatory office for pharmaceuticals, the FDA, which was empowered to license medicines subject to certain safety standards. US drug companies had to show only the safety of their new products before 1960. However, in 1962 the US Kefauver Harris Amendments followed as a response to the Thalidomide disaster and introduced an additional proof-of-efficacy requirement that was not present before. Other countries in Europe aligned their marketing authorization procedures for increased safety and efficacy only in late 1960s and early 1970s (Permanand 2006).

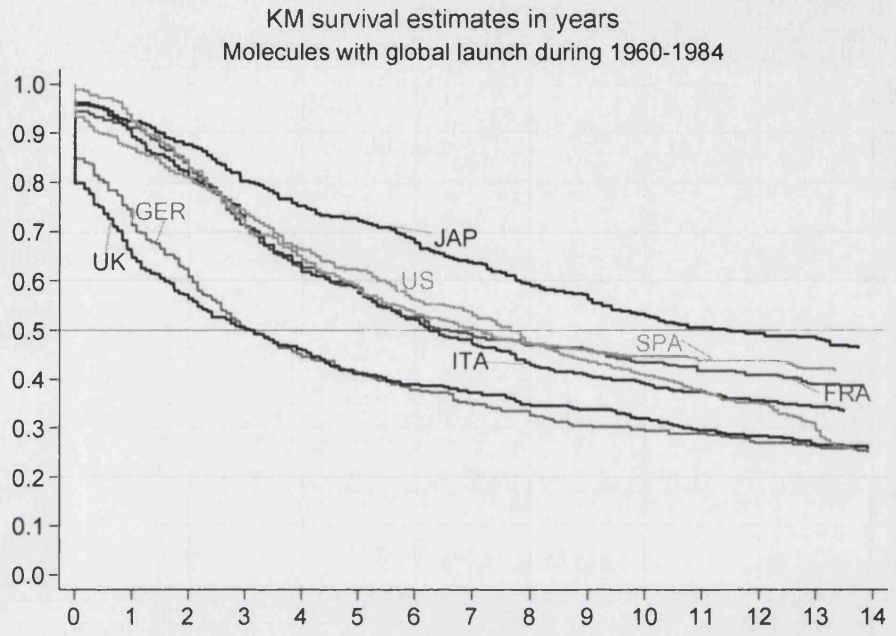
The debate about launch delays extends back to 1960s when the main concern was the significant US drug lag compared to the main EU markets, mainly as a result of the more stringent US regulations. Wardell, a pharmacologist, coined the term "drug lag" and increased awareness of the unavailability of new drugs in the US, and stressed that the delays affected therapeutically important drugs as well (Wardell 1973; Wardell 1974; Wardell 1978). Later studies by Grabowski (1980), Berlin and Jonsson (1986) and Kaitin (1989) confirmed findings of Wardell (Grabowski 1980; Berlin and Jonsson 1986; Kaitin, Mattison et al. 1989).

The survival estimates in this study for molecules that launched first during 1960-1984 confirm findings of the early literature that the US market was relatively disadvantaged for the timely adoption of pharmaceutical innovations as a result of much stricter requirements for regulatory approval. The survival graph in Figure 2.2 shows *S(t),* the probability that molecule launch in a given country occurs after *t* years following global launch, conditional on the fact that the molecule has not launched in that country up to time *t*. Hence, it takes longer for countries with a higher survival curve to adopt new pharmaceutical innovations. The median survival value is given where $\hat{S}(t) = 0.5$.

During 1960-1984, Europe is found to be leading in the introduction of pharmaceutical innovation. As expected, free price countries such as the UK and Germany are leading markets, with a median delay of 3 years and are followed by Italy, France and Spain with a corresponding lag of 3.5−4 years. The US lags behind the slowest European market by about half a year. Japan has the most dramatic delay of 12 years, which can

be attributed to geographical barriers and predominantly domestic nature of the market, especially in a period when the global expansion of pharmaceutical corporations was relatively limited.

Figure 2.2 Survival Estimates: 1960-1984



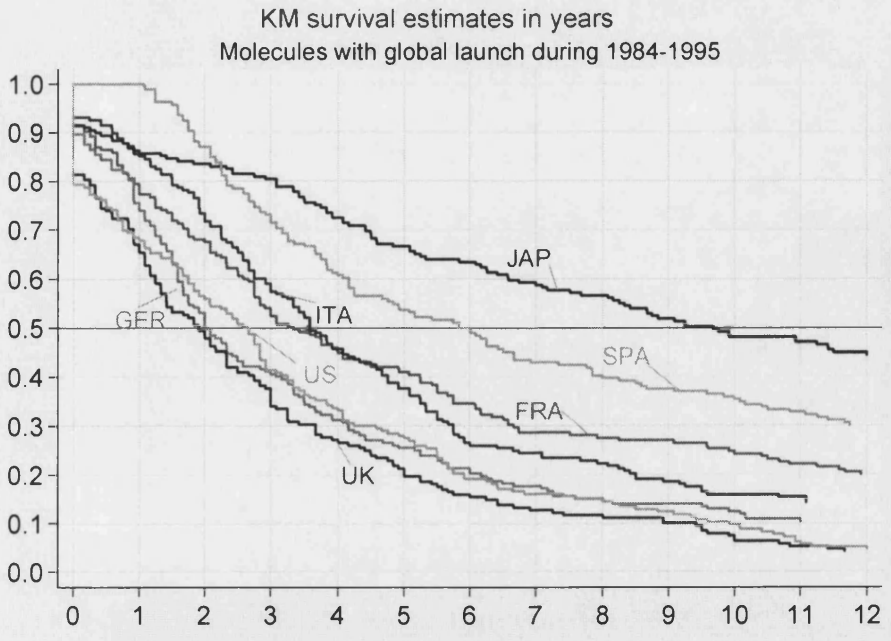
2.3.1.2 1984-1995: The US Hatch-Waxman Act and Stimulus for Innovation

The Hatch Waxman Act, also known as the Drug Price Competition and Patent Term Restoration Act of 1984, was enacted to compensate for the loss in effective patent life during drug development. The Act extended pharmaceutical patents for the time lost in clinical testing and regulatory review, but the entire patent term restored was restricted to 5 years and the term of the restored patent following FDA approval was restricted to 14 years. In addition, the Act introduced a five-year market exclusivity period for NMEs such that once an NME is approved a generic manufacturer cannot submit an application until 5 years after the approval of the pioneer and thus cannot enter the market for at least 5 years. These amendments enabled pharmaceutical innovators to recoup some of the revenue losses due to regulatory delay after 1962. The main aim of the Act, however, was to maintain incentives for innovation while ensuring quick generic entry. The Act substantially facilitated generic entry by eliminating the entry barrier of duplicative testing required for generic substitutes. Generic entrants would only need to submit an Abbreviated New Drug Application (ANDA) to demonstrate the bioequivalence of the generic drug to the original obviating the need to duplicate the

safety and efficacy efforts of the originator firm (Berlin and Jonsson 1986). This would allow the generic manufacturer to put its FDA-approved drug on the market as soon as the patent expires. The Act increased the availability of generics and reduced the market share of innovative companies; however, data from the literature suggests that R&D funding and R&D intensity increased substantially after the Act. The impact on the brand-name drugs, therefore, has remained somewhat contentious as it is not known exactly to what extent the stimulation for innovation accounts for the increase in innovative activity post 1984 (Branes 2007).

Survival estimates in this study indicate a stark improvement in the US for the timing of new product launches vis-à-vis Europe (Figure 2.3). The median delay in the US decreased from about 8 years to 3 years following the enactment of the Act whereas the corresponding decrease in the leading markets of the UK and Germany was on the order of one year only. While the US was the second slowest market to adopt new pharmaceutical molecules in 1960-1984, after the 1984 Act the US becomes one of the leading markets along with the UK and Germany. The estimates present a clear indication that the 1984 Act has generated a more favourable environment for market entry in the US and suggests an increase in overall R&D activity in the US pharmaceutical industry.

Figure 2.3 Survival Estimates: 1984 - 1995



The remaining markets in Europe also experience faster introductions after 1984. In particular, the medians in France and Italy decrease by 3 years (to about 3.5 years). The one-year reduction in the Spanish median delay is more modest and can be partially attributed to the lack of product patent protection for new pharmaceuticals before ratification of the TRIPS Agreement in 1995. Overall, Spain and Japan emerge as the slowest adopters following the 1984 Act. Thomas (2001) who analyzes the Japanese lag during 1981-1993 posits that the core factor driving exclusion from Japan is the distinctive nature of the clinical trial system. Foreign firms face an asymmetric cost with respect to Japanese firms since they have to test their products twice. The second factor that drives the exclusion of foreign firms and delays are the price regulations since 1981 that sharply lowered launch prices and the life cycle sales of drugs launched into Japan (Thomas 2001).

Patent term restoration in Europe was enacted only eight years following the 1984 Act in the US. In 1992, Supplementary Protection Certificate (SPC) extended the protection period of pharmaceutical products in the European Community by 5 years following patent-expiry or 15 years of protection from the date of first market authorization in the European Community, instead of twenty years after patent application as under the European Patent Convention[33]. This prolonged the profit life of products as drug sales are generally highest during the period of market exclusivity. In addition, the SPC prevented generic companies from engaging in R&D prior to patent expiry, which essentially ensured a longer shelf-life for branded products and provided stimulus for innovation. The relative delay in providing financial stimulus for innovation through patent term restoration in the EU could be an additional factor that explains the drastic improvement in the timing of new product launches in the US vis-à-vis Europe during 1984-1995.

2.3.1.3 1995-2008: EMEA and Harmonization across the Globe

The set up of a single market in 1993 and a common currency in 1999 (when exchange rates were pegged) ensured free movement of people, goods and services within the EU. Since then market authorization has been streamlined by the establishment of the EMEA in 1995 although a complete harmonization of the pharmaceutical market has not taken place. This was a significant step to speed approval times across Europe

[33] The SPC became effective on Jan 1993 and applied to drugs granted market authorization in the EU after Jan 1985.

which had begun to suffer from increasing number of applications as the industry grew and technical and scientific issues became more complex. In addition, EU Directive 2004/27/EC introduced a uniform level of data protection for 10 years across the EU and precluded the launch of the generic copy until the expiry of the 10-year period.

A centralized approval procedure, which grants a Community-wide authorization valid in all Member States, would increase efficiency by obviating the duplication of effort through a single market authorization process and saving an annual expenditure of $350m by drug firms to get separate approvals from individual member countries (Annon 1994). The centralized procedure, however, does not apply to all products. It is mandatory for all biotechnology processes and optional for innovative chemical drugs provided the product offers a significant therapeutic, scientific or technical innovation[34].

After 1990, the pharmaceutical industry has witnessed further efforts of harmonisations. The Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) in 1994 strengthened intellectual property rights and provided significant financial incentives for companies by blocking generic competition until the expiry of the 20 years patent life and by extending the scope of patent protection both to products and processes (WTO OMC 2003). Similarly, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has aimed to achieve greater harmonisation in the application of technical guidelines and requirements for product registration across the EU, US and Japan to reduce or obviate the need of duplicative testing in the R&D stage[35].

Figure 2.4 shows that the median delays continued to decrease throughout 1995-2008 as a response to the harmonization efforts across the biggest 7 pharmaceutical markets, yet the differential delays have not been eliminated totally[36]. Most of the molecules launch immediately in the US followed by launch in the free-priced European markets of Germany and the UK within one year. The US emerges as the most favourable market because of high profit potentials. This is both because the US has the largest market size and a more liberal pricing environment compared to other OECD markets that employ

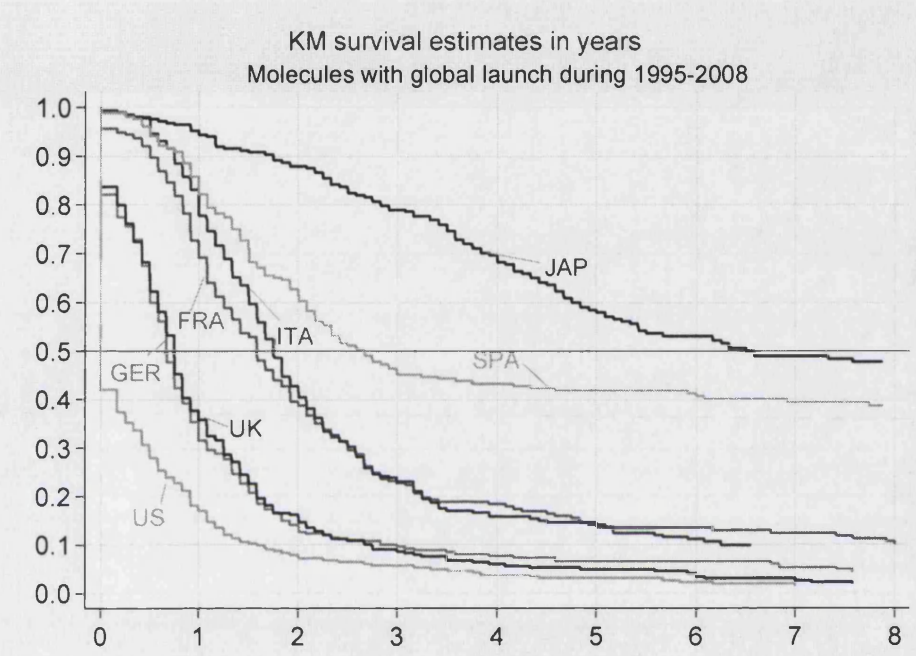
[34] http://www.emea.europa.eu/

[35] http://www.ich.org

[36] Log-rank test for equality of survivor functions indicate that the difference in median delays between countries is significant (p-value: 0.0000). In addition, significant heterogeneity exists with respect to the ATC group (p-value: 0.0021), which implies that the relative delays vary across ATC groups.

some form of price control, either in the form of statutory pricing whereby the price is set on a regulatory basis or through price negotiations (Vogler 2008). Stringent price controls have been criticized for having negative implications on the extent and timing of launch via knock-on effects on foreign markets through external referencing and parallel trade within the EU; however, the available evidence is limited (Danzon and Epstein 2005; Kyle 2007; Danzon and Epstein 2008).

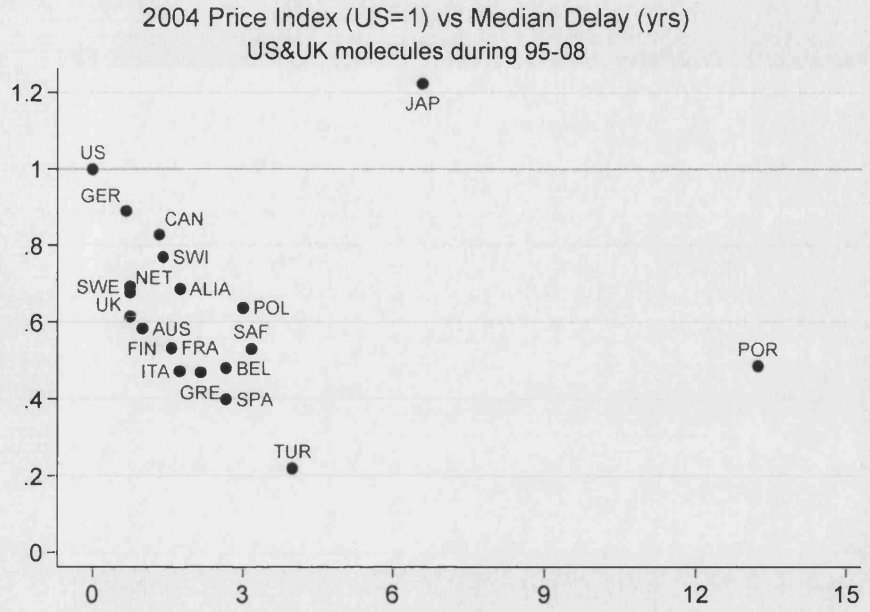
Figure 2.4 Survival Estimates: 1995-2008



The relative launch delays in Europe suggest an ordering with respect to price levels of pharmaceutical products. Figure 2.5 illustrates the correlation between median delays and the bilateral price indexes with respect to US prices for 2004. The correlation is -0.47 and is significant at the 0.01 level. France and Italy seem to have a comparable speed of launch with a median delay of around two years. The median lag in Spain has decreased compared to 1984-1995 but it still lags about a year behind France and Italy. The lack of product patent protection for new pharmaceuticals before EU membership contributes to launch delays in Spain. EU accession in 1986 required Spain to comply with the European Patent Convention (EPC), which allowed the patentability of both products and processes.

Figure 2.5 Bilateral Price Indexes with Respect to US Prices vs. Median Delays

(for ethical branded products in the retail sector)



Note: Bilateral price indexes are calculated by considering common molecules in the US and the respective country, prices are weighted by the US Volume[37]

Spain enacted a new patent law in 1986 that introduced patent protection for pharmaceuticals. However, effective patentability was delayed until 7 October 1992 through Reservation under Article 167 of the EPC, which essentially meant that pharmaceutical and chemical products could not be patented in Spain prior to 7 October 1992. In 1995, Spain ratified the TRIPS Agreement, which substantially changed the patent protection landscape[38]. In addition, Spain is one of the major parallel exporters in the EU due to its relatively lower drug prices, which are further pushed downwards by unilateral price cuts imposed on pharmaceutical prices. The delay in Spain, therefore, is consistent with pharmaceutical firm strategies to avoid parallel trade as suggested by Kyle (2007).

[37] ALIA: Australia; AUS: Austria; CAN: Canada; FIN: Finland; FRA: France; GER: Germany; GRE: Greece; ITA: Italy; JAP: Japan; NET: Netherlands; POL: Poland; POR: Portugal; TUR: Turkey; SAF: South Africa; SPA: Spain; SWE: Sweden; SWI: Switzerland

[38] https://www.eversheds.com/uk/Home/Articles/index1.page?ArticleID=templatedata\Eversheds\articles\data\en\Healthcare\BioBrief_Stop_press_Direct_applicability_in_Spain_of_patent_provisions_of_the_TRIPS_Agreement

The Japanese drug lag extends to this period as well although the median Japanese delay decreases by two years with respect to the previous period. This is paradoxical given the international competitiveness of numerous Japanese high-tech industries including electronics and automobiles during 1990s. The Japanese pharmaceutical market is the second largest market in the world and offers a great profit potential because of a large market size and relatively high drug prices. Nevertheless, the Japanese pharmaceutical industry still remains predominantly domestic and uncompetitive.

Japanese regulations for new drug approval have required Japanese clinical data for evaluating the efficacy and safety of the drug even if foreign clinical data are available due to racial and ethnic variations in responses to medicines. In the past, all three phases of clinical trials had to be carried out on the Japanese population, which has driven launch delays in addition to other factors such as language barriers and longer times for patient enrolment in clinical trials. In 1998, Japan adopted the ICH E5 guideline entitled "Ethnic Factors in the Acceptability of Foreign Clinical Data" that recommends the use of foreign clinical data for new drug approval if there is one additional bridging study[39] showing that the drug will behave similarly in the Japanese population. According to Uyama et al. (2005) new drug approvals based on a bridging strategy in Japan have increased from 3.2% in 1999 to 25% in 2003. Tabata and Albani (2008) report that companies are increasingly trying to leverage their operations globally in order to take advantage of the Japanese efforts to comply with the trend for globalising clinical trials (Tabata and Albani 2008). These developments suggest that the drug lag in Japan can decrease over the next years (Uyama, Shibata et al. 2005).

Ranking countries by median lags, countries may be characterised as leaders (the US, UK, Germany, Sweden, Netherlands, Finland, Austria, Switzerland) and laggards (Belgium, Greece, South Africa, Poland, Portugal, and Turkey). The remaining countries (France, Canada, Italy, Australia, and Spain) rank as intermediaries with the rank dependant on the period and extent of global launch. The laggards and leaders, as defined by countries with median lags above and below the overall delays, are similar for the global and the US&UK molecules; however, the extent of the relative lag is shorter for the truly global molecules as is expected because global molecules have

[39] A bridging study aims to confirm that the efficacy, safety and dose-response relationships of the drug in the new population are similar to those in the population evaluated in the foreign studies

diffused to all markets and have non-censored survival times. Similarly, launch in all markets may indicate higher therapeutic or commercial importance at the product level.

2.3.1.4 EMEA Sub-Analysis

Differences in the survival behaviour among the EU markets in Figure 2.4 indicate that pharmaceutical firms have adopted different launch strategies across markets in the EU and that efforts of harmonization in market authorization procedures have not eliminated the differentials in timing of launch across European countries. I carry out a sub-analysis for the EU countries[40] to further investigate the impact of the establishment of a centralized regulatory procedure in the EU. In order to compare relative delays for molecules that obtained centralized approval (central molecules) with those that did not (non-central molecules), data was collected for all centrally approved molecules from the EMEA website (the EMEA publishes information following the grant of a Marketing Authorization as a European Public Assessment Report[41]). This information was combined with the IMS database to estimate delays within the EU for molecules with a first global launch post-1995.

There is a statistically significant difference in launch behaviours between the central and non-central molecules (p-value: 0.000 for the test of the null hypothesis that the survival behaviours of EMEA and non-EMEA molecules are identical). The effectiveness of a more streamlined authorization is demonstrated by the lower variation in launch timing for EMEA molecules compared to molecules that did not go through the centralized procedure. The median delay for non-central molecules is greater by more than 2 years compared to the median delay of central molecules which is on the order of one year.

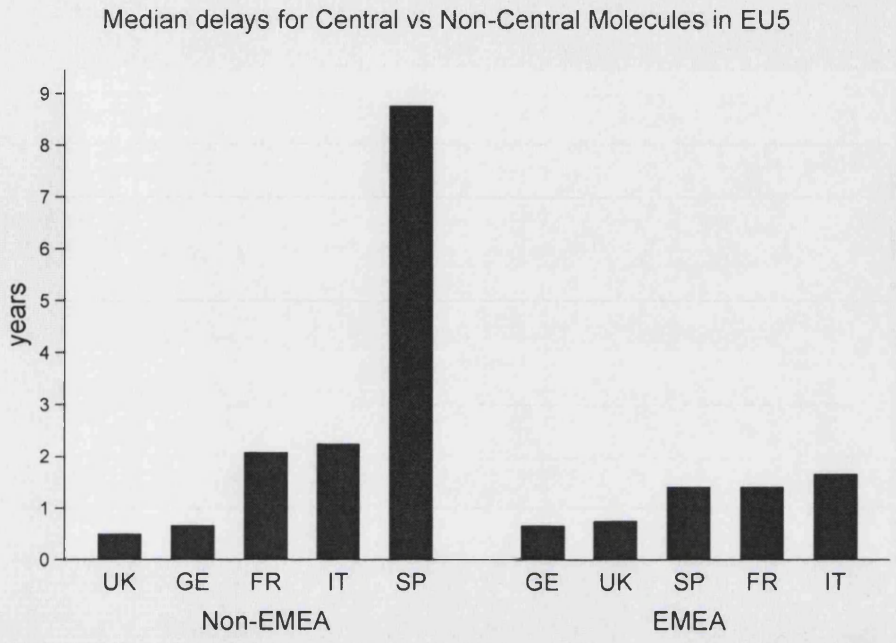
The faster diffusion of centrally approved molecules can be attributed to the elimination of differentials in regulatory approval times as well as a potentially higher therapeutic/commercial value of the centrally approved drugs (Figure 2.6). Central approval speeds up the introduction of molecules in laggard countries such as France, Italy and Spain. Spain exhibits the most dramatic reduction in median delays -a reduction from 5 years to 1.5 years- among the five main European pharmaceutical

[40] Austria, Belgium, Finland, France, Germany, Italy, Netherlands, Poland, Portugal, Spain, Sweden, UK

[41] http://www.emea.europa.eu/htms/human/epar/a.htm

markets due to central approval. For France and Italy the reduction is on the order of half a year only.

Figure 2.6 Delays with respect to central vs. non-central approval in the EU



(Kaplan-Meier estimate for Spain not available, the restricted mean which provides a lower bound for the median is reported)

The centralized EU procedure is compulsory for all medicinal products derived from biotechnology and other high technology processes. If the product does not belong to the designated disease categories[42] for central approval, companies can submit an application for a centralized marketing authorization, provided the product offers a significant therapeutic, scientific or technical innovation[43]. A more homogenous cross-country launch for central molecules across the EU indicates that on average European patients have more equitable access to drugs that have priority from a health policy perspective-at least to the extent that these drugs are diffused at comparable times (the take-up and access post-launch may introduce further differentials in access due to differences in reimbursement policies as well as cultural factors).

[42] These categories include all human medicines intended for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases, and all designated orphan medicines intended for the treatment of rare diseases

[43] http://www.emea.europa.eu/

2.3.2 Trends in the Adoption of Pharmaceutical Imitation

The lags in generic entry across countries depend on differentials in patent expiry dates or market exclusivity as well as originator firm strategies to block or delay generic competition. Due to unavailability of data to control for patent expiry dates or originator firm actions, the estimates provide generic lags as the time elapse between the first global generic product launch and local generic launch for a given molecule-country pair. This measure cannot assess to what extent generic entry is delayed following patent expiry and hence provides only a relative measure across countries.

Evolution of Median Delays over Decades

The trend in overall median delays for generic molecules that launched both in the US&UK from 1960 to 2008 is similar to the case in the cross-country diffusion of pharmaceutical innovation; the diffusion of imitative pharmaceutical has accelerated over time (see Figure 2.7). In each period, medians are reduced by half compared to the previous period. The overall median delay has decreased from 26 to 14.5 years from 1960-1984 to 1984-1995 and to 8 years during 1995-2008. The confidence intervals of medians estimated by Stata are non-overlapping, which suggests that the difference in median delays is significant (see Table 2.7). Next, I test for the significance of the impact of first generic launch period by semi-parametric estimation.

Figure 2.7 Overall median delays of generics with respect to period of global launch

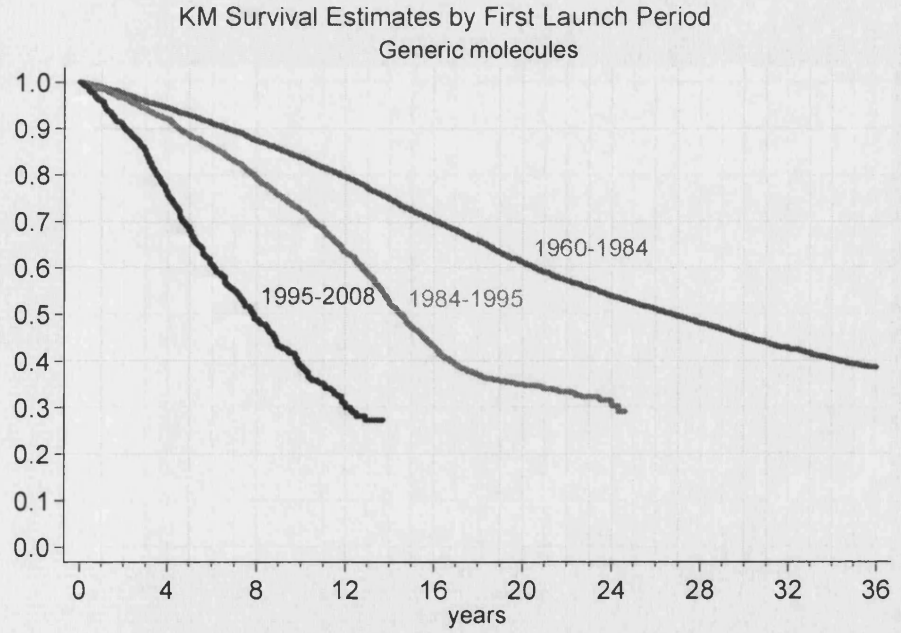


Table 2.7 Median delays and confidence intervals by period of first launch (generic molecules)

Period	*Subjects*	*Median*	*Std. Err.*	*[95% Conf. Interval]*	
1960-1984	3924	26.83	0.54	25.75	27.83
1984-1995	1688	14.58	0.23	14.00	14.92
1995-2008	869	7.83	0.31	7.33	8.58

Cox Proportional Hazard Model: Test of Survival Trend Significance

In parallel to the case with innovative molecules, fixed and random effect Cox models were estimated for generic drugs using the same specifications in Section 2.3.1. Table 2.8 presents the estimates for the Fixed Effects Cox Estimates. First global generic adoption in 1960-1984 has a hazard ratio of 0.641, and therefore, is associated with a 46% in the hazard compared to molecules that had first global adoption during 1984-1995. Similarly, first generic launch in 1995-2008 is associated with a 3.104 faster hazard rate compared to first generic launch in 1960-1984.

Table 2.8 Cox regression with country fixed effects: generics

Variables	*Hazard Ratio*	*Std Err*	*z*	*P>|z|*	*[95% Conf. Int.]*	
Global launch in 60-84	0.641	0.026	-10.89	0.000	0.592	0.694
Global launch in 95-08	3.104	0.179	19.69	0.000	2.773	3.474
Austria	0.777	0.085	-2.3	0.021	0.627	0.963
Belgium	0.602	0.068	-4.47	0.000	0.482	0.752
Canada	1.399	0.146	3.21	0.001	1.140	1.718
Finland	0.738	0.083	-2.71	0.007	0.592	0.919
France	0.781	0.084	-2.31	0.021	0.632	0.963
Germany	1.557	0.162	4.26	0.000	1.270	1.909
Greece	0.825	0.092	-1.73	0.084	0.663	1.026
Italy	0.836	0.093	-1.61	0.108	0.672	1.040
Japan	0.836	0.095	-1.59	0.113	0.669	1.043
Netherlands	0.811	0.090	-1.88	0.060	0.652	1.009
Poland	1.086	0.115	0.78	0.438	0.882	1.338
Portugal	0.655	0.075	-3.68	0.000	0.523	0.821
S.Africa	0.720	0.084	-2.83	0.005	0.574	0.904
Spain	0.786	0.089	-2.11	0.035	0.629	0.983
Sweden	0.607	0.069	-4.37	0.000	0.485	0.759
Switzerland	0.639	0.073	-3.92	0.000	0.511	0.800
Turkey	0.857	0.096	-1.37	0.170	0.687	1.069
UK	2.011	0.202	6.94	0.000	1.651	2.449
US	2.130	0.215	7.51	0.000	1.748	2.595

Table 2.9 shows the estimates for the random effects Cox model. The estimates for the hazard ratio are similar to the estimates in the random effects model, 0.642 and 3.097 for first generic launch in 1960-1984 and respectively 1995-2008. Overall, the reduction in the adoption differentials for generics is also statistically significant. The Hausman test comparing fixed and random effects indicates that the shared frailty specification is preferable (p-value 0.0784). The acceleration in generic adoption over time can be mainly attributed to new regulations in the US and EU that have enabled generic drug development before patent expiry and reduced capital requirements by obviating the need to reproduce data from clinical trials.

Table 2.9 Cox regression with shared frailty specification for generics

Variables	*Hazard Ratio*	*Std Err*	*z*	*P>|z|*	*[95% Conf. Interval]*	
Global launch in 60-84	0.642	0.026	-10.84	0.000	0.593	0.696
Global launch in 95-08	3.097	0.178	19.66	0.000	2.767	3.466
Theta	0.139	0.045				

Likelihood-ratio test of theta=0: chibar2(01) = 352.99 Prob>=chibar2 = 0.000

Note: standard errors of hazard ratios are conditional on theta.

Difference-in-Differences Analysis for Generics

Table 2.10 and Table 2.11 present the corresponding DiD estimates for the policy change effects in 1984 and 1995 on the adoption of generic competition. Estimated regression models assume the same specification as outlined in Section 2.2.2.3 and 2.3.1. The impact of the 1984 Act on the adoption of generics in the US is quantified by the coefficient of the DiD estimator *US_d_1984*, which is negative (indicating a reduction in the relative adoption delay in the US) and highly significant. This is expected as the Bolar provisions in 1984 were highly effective in decreasing barriers to entry for generics.

The impact of the EMEA on generic adoption (parameter *EU_d_1995* in Table 2.11) indicates a decrease in the adoption time; however, the effect is not significant. In the case of new molecules, excluding the US from the control group changed the significance of the DiD estimate. However, in the case of generics, excluding the US makes no difference. The establishment of the EMEA did not reduce the barriers to entry as the Hatch-Waxman did in the US in 1984. Similar Bolar provisions in the EU

were only accepted in 2004. Therefore, it is not paradoxical that the DiD estimate for the policy change in 1995 is not significant in the case of generics.

Table 2.10 DiD Analysis for 1984 US Hatch Waxman Act (Generics)

Variables	*y=ln(t)*	*y=t*
US	0.335** [0.13]	1.763 [1.29]
d_1984	0.691*** [0.05]	8.128*** [0.39]
US_d_1984	-0.733*** [0.13]	-7.112*** [1.24]
Country Effects	Yes	Yes
Number of Observations	4846	4846
Log Likelihood	-6193.07	-18664.4
p-value	0.000	0.000
Akaike Info Criteria	12430.13	37372.71
Bayesian Info Criteria	12572.82	37515.4

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

Table 2.11 DiD Analysis for the Impact of EMEA in EU (Generics)

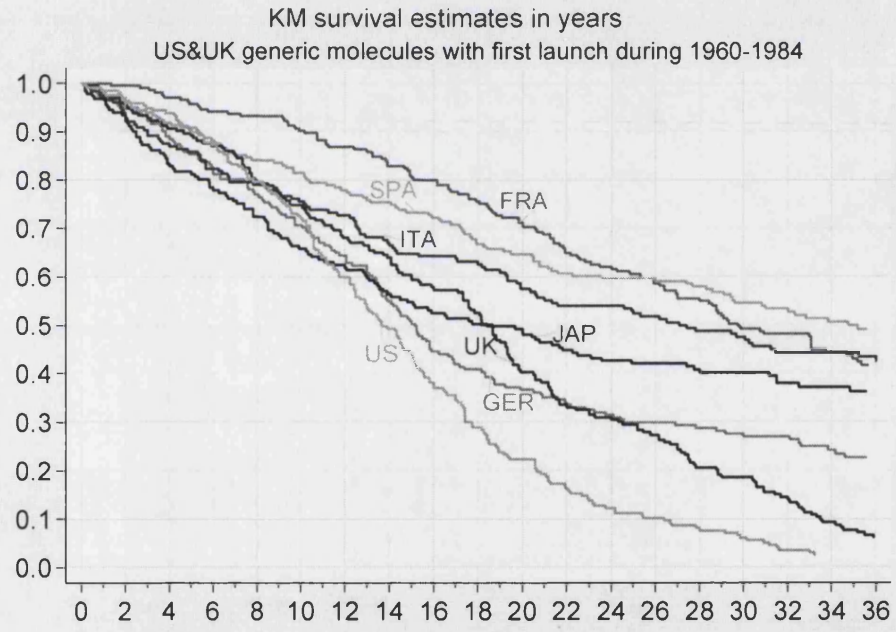
Variables	*DID*	*DID (excluding US)*
EU	-0.227* [0.09]	-0.233* [0.09]
d_1995	-0.295*** [0.04]	-0.310*** [0.04]
EU_d_1995	-0.023 [0.05]	-0.008 [0.06]
Country Effects	Yes	Yes
Number of Observations	4846	4618
Log Likelihood	-6251.86	-5952.06
p-value	0.000	0.000
Akaike Info Criteria	12547.73	11946.12
Bayesian Info Criteria	12690.42	12081.31

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

2.3.2.1 1960-1984: Stringency in MA Regulations and the US drug lag

In the previous sections, significant lags in the US were observed for new molecules. As Figure 2.8 2.8 shows, the US exhibits no drug lag with respect to the adoption of first generics. Based on a cross-country perspective, Italy, Spain and France adopt generics latest, and are surpassed by Germany and the UK. The delay in generic adoption in Spain and France is considerable compared to the free-priced EU markets (the UK and Germany). This pattern in Europe is broadly in line with the pattern for innovative pharmaceuticals; except for the fact that UK lags behind Germany during this period by about 3 years (see Table B.5 in Appendix B for the exact figures). Also, in contrast to the case for innovative molecules, adoption of generic competition in Japan is relatively fast during this period.

Figure 2.8 Survival Estimates for Generics: 1960-1984



2.3.2.2 1984-1995: The Hatch-Waxman Act and Improved Generic Access in the US

Although there is no indication that US is lagging in the introduction of generic products during 1960-1984, the Drug Price Competition and Patent Term Restoration Act of 1984 sought to improve generic entry while ensuring adequate return for innovator firms through patent restoration (Wittner 2004). As an immediate benefit, the 1984 Act allowed generic manufacturers to develop generic drugs before patent expiry

of the originator product (often referred to as the "Bolar" clause)[44]. In addition, the Act reduced barriers to generic entry by substantially reducing development costs. Generic producers were allowed to reference the originator's safety and efficacy data obviating the need to repeat the same tests. In addition, the Act introduced 180 days of market exclusivity period to the first company to file a new generic application (known as ANDA, Abridged New Drug Application).

Figure 2.9 Survival Estimates for Generics: 1984-1995

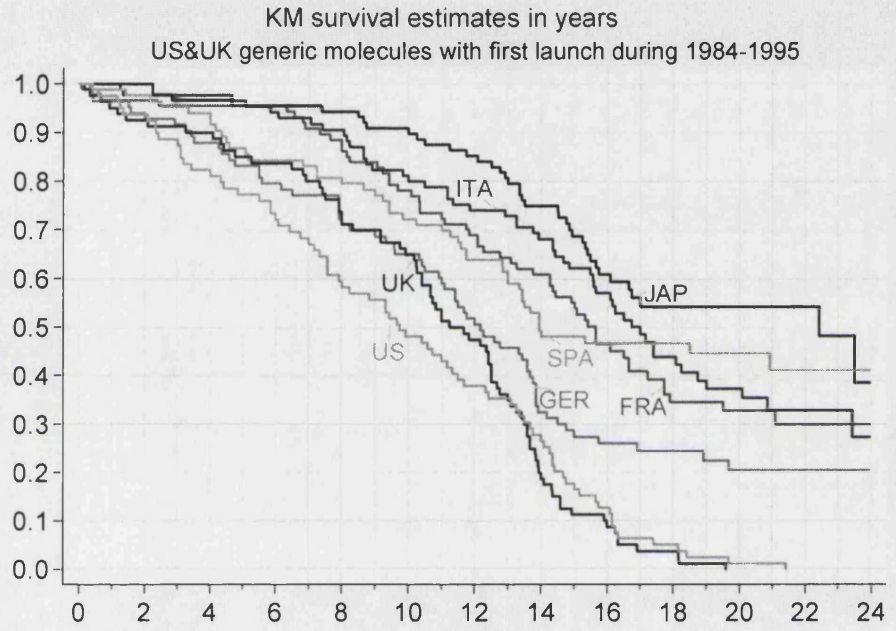


Figure 2.9 shows the pattern of differential lags during 1984-1995. Compared to the 1960-1984 three main differences emerge. First, following the provisions for quicker generic entry in the Hatch-Waxman Act, the median delay in the US is reduced by 4 years (from 14 years to about 10 years). Second, the Japanese lag for generics increases by 4 years. Third, UK and Germany show equally fast generic adoption with a median lag on the order of 11-12 years. Finally, France, Italy and Spain follow with a median delay of 14-17 years.

[44] The name is derived from a landmark case between Roche and the generic companies Bolar. Bolar won the right to start developing the generic copy of Roche's patented compound Flurazepam Hydrochloride prior to its patent expiry, which was incorporated into the 1984 Act.

2.3.2.3 1995-2008: EMEA and New Generic Legislations in Europe

The period from 1995 to 2008 witnessed important regulatory changes in generic legislations both in the US and Europe. Europe followed the US in providing incentives for generic development and timely market access in Europe. The US, on the other hand, focused mainly on the prevention of originator firm strategies to delay or block generic competition.

Changes in the US Generic Legislation

Two revisions (McCain-Schumer legislation in 2002, Gregg-Schumer Act in 2003) to Hatch-Waxman Act in the US sought to improve the balance between the needs of the branded companies and those of the generic companies. First, the new revisions set up a new mechanism to prevent the inclusion of frivolous patents or those filed at the last moment as a blocking mechanism. Second, the new legislation addressed the use of 180-day exclusivity period by generic companies for special arrangements with originators as a means to prevent market entry of other generics[45]. Gregg-Schumer revisions included "forfeiture" provisions which put the generic company under risk of losing the exclusivity if found to have made such an arrangement.

Changes in the European Generic Legislation

Europe's fragmented market structure has presented a major barrier to generic growth compared to the US market where federal law applies uniformly across different states. Directive 2004/27/EC has aimed to remove some of these barriers by updating Directive 2001/83. As with the US Hatch-Waxman Act, the legislation was intended to balance the needs of the branded pharmaceutical companies and generics companies. The overall body of EU law governing the manufacture and trade in pharmaceuticals (Directive 2001/83) had flows such as the lack of a generic-product definition and allowed branded companies to withdraw reference products before generic entry.

The new laws introduced a specific "generic" definition. One of the most important aspects for generics companies was the "Bolar" clause permitting generic companies to

[45] According to the 1984 Act, if the first generic company chose not to market the generic copy, all other generic competitors from the market would be excluded and all competition would be blocked for a period of 180 days. Authorized generics, copies made under license from the innovator companies, were introduced whereby the originator receives royalties on sales in return. For example, Par Pharma's generic version of Glaxo's Paxil (Paroxetine) was launched with Glaxo's approval even though Apotex had obtained six-month exclusivity for its own generic.

do their own development work within the EU during the period of patent protection for the original molecule. The practical impact of the clause on the timing of product launches may be minimal because wherever the development is carried out, generics cannot be launched prior to patent expiry. The main benefit however is that companies could maintain generic drug development in the EU[46].

Under the new legislation, the same product can be used as a reference product for generics everywhere in the EU even if not registered in particular countries. This is a small step towards unification of European generic legislation. In addition, if originator companies withdraw a brand before any generic versions are marketed, the generics can still use it as a reference product. Finally, the establishment of the EMEA in 1995 had little direct impact on generics companies. However, the centralized procedure is open to generics provided that the original is approved through the centralized system (Wittner 2004) .

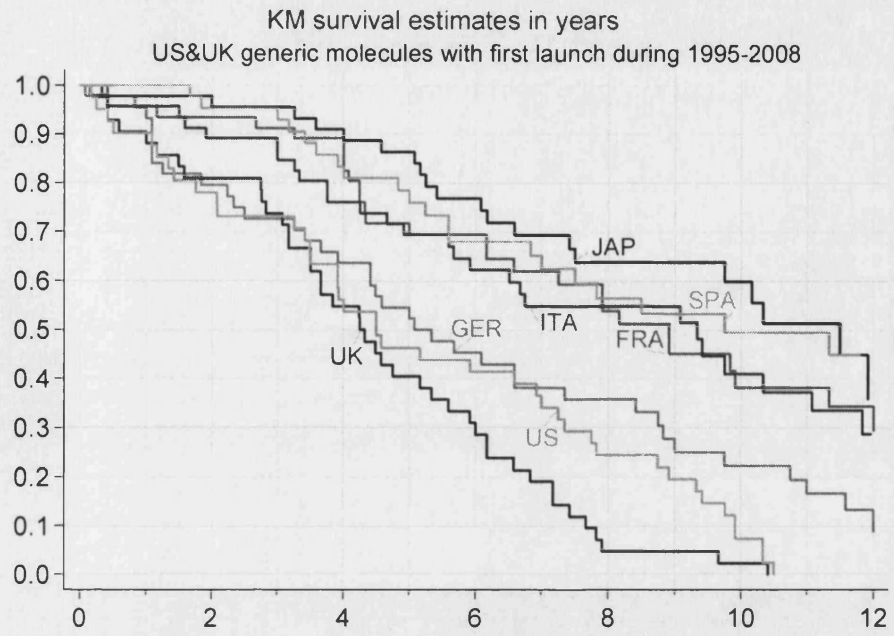
Generic Lags across Markets follow the Pattern of Non-Generic Lags

Figure 2.10 demonstrates that the pattern of launch for the first imitative generic product is quite similar to the pattern for innovative molecules[47]. New generic legislations have proven effective in the EU in further reducing the generic lag although it is hard to quantify to what extent the reductions are triggered by new legislations. The fastest adopters are as usual markets with relatively high originator prices (the US, UK and Germany) that offer higher profit prospects for imitative products. The median delay for the leaders is on the order of 4-5 years, with a reduction of 5-6 years compared to 1984-1995. More regulated markets (Italy, Spain and France) lag by about 5 years behind the leaders, with a median delay of 9-10 years (which is a significant reduction from 14-17 years in 1984-1995). Japanese lag for the adoption of generic competition is not as dramatic as for innovative molecules; however, Japan is still the slowest market among the biggest seven markets with a median delay of 11 years.

[46] As mentioned before, the SPC had prevented generic companies from engaging in R&D prior to patent expiry.

[47] Similar to the non-generic case, equality by country, atc1, form1 and first launch period rejected (p-value < 0.001 for all).

Figure 2.10 Survival Estimates for Generics: 1995-2008



Similar survival profiles for new molecules and generic products indicate that the negative impact of price controls on the launch timing of pharmaceutical innovation has spillover effects on the adoption of generic competition. The bottom-line is that regulated markets not only access innovation later, but also face temporal disadvantage in terms of their access to cost-effective generic products. To what extent this is balanced by lower branded prices remains an open question for further exploration.

2.4 CONCLUSIONS

This chapter has sought to test the stylized facts suggested by earlier empirical work on regulation and the adoption of pharmaceutical innovation and generic competition. To do so, this chapter provided an overview of the evolution of the drug lag for new innovative molecules and first generic products for off-patent molecules across the main OECD markets. The regulatory environment and relative launch times of new molecules and first generic copies were analyzed using non-parametric Kaplan-Meier survival estimates for three periods over 1960-2008, which were defined based on two landmark events in the regulatory history of pharmaceutical products: the 1984 Hatch-Waxman Act in the US and the establishment of a central regulatory agency in Europe in 1995. This is the first study to provide a descriptive evolution of relative lags across a number

of markets over a lengthy period of time and a comprehensive set of molecules, both for innovative products and imitative generic copies. The significance of the findings in the Kaplan-Meier analysis were further assessed more rigorously by Cox PH models and difference-in-difference analysis.

Lower transaction costs due to reductions in geographical barriers and lower regulatory costs (harmonized market authorization procedures, strengthened IP rights, patent term restorations) have exerted a downward pressure over time on median delays in individual countries as well as overall delays across the main OECD markets. All markets experience a decreasing trend over time for median delays following global launch. With the wider use of the centralized procedure over the coming years, the delays in the diffusion of pharmaceutical innovation across the EU may be further smoothed out. However, the relative lags across countries remain significant both for new molecules and for generic products due to various pricing and reimbursement regulations.

A somewhat paradoxical important finding is that the negative impact of price controls on new molecules translates to delayed generic availability, which suggests that regulation not only delays patient access to new pharmaceutical technologies but also creates trade-off between existing competition and potential competition. While lower prices may increase the extent of competition between existing rivals, they may also consitute a barrier to entry for potential generic competiton. Delaying or blocking potential competition implies opportunity costs for governments through foregone savings. Assessing the impact on overall welfare, however, would require a comparison of savings from lower branded product prices and savings foregone due to late generic launch and possibly lower generic penetration. Relative delays in the diffusion of generics are expected to decrease further because of the new European legislation in 2004 and the push for genericization as a cost-containment mechanism in government policies facing economic challenges of the recent financial crisis.

Globally, the relative lags exhibit a change in the geographical pattern of lags over time. The US lag back in 1960s has switched to more price stringent European markets throughout 1960-2008. Relatively free-priced European markets of Germany and the UK[48], which also have strong local pharmaceutical industries, lead in the EU as the

[48] However, prices may be indirectly affected through regulations in other parts of the market. In the UK profits are regulated through the PPRS (Pharmaceutical Price Regulation Scheme) and products are subject to NICE appraisals for Cost-Effectiveness ("the fourth hurdle"). Flexible Pricing schemes

fastest adopters of pharmaceutical innovation (and imitation). Product launch strategically takes place first in higher-priced EU markets as a result of threat of arbitrage and price dependency across the member states, which puts European markets with low prices and/or small market sizes such as Spain and Portugal at a disadvantage. Paradoxically, the Japanese market with its large market size and relatively high prices remains a laggard throughout 1960-2008. The idiosyncratic nature of clinical trial requirements in Japan has been the major driver of asymmetric costs for foreign pharmaceutical firms. Harmonization efforts on foreign clinical data use seem to be taking effect slowly and expected future rise in the use of the bridging strategy may further reduce the Japanese drug lag in the upcoming years.

The R&D activity of leading pharmaceutical companies is largely carried out in the major OECD markets. Reducing delays in these markets will increase the appropriability of R&D investments and stimulate further innovation contributing to dynamic efficiency over the long run. On the other hand, new pharmaceutical technologies impose additional pressure on the tight health care budgets and quick diffusion of new technologies with uncertain benefits could lead to inefficiencies in the provision of health care (Garber and Skinner 2008). The introduction of new drugs in individual markets, therefore, should be balanced out with the expansion of drug expenditure and the evidence of cost-effectiveness. From a cross-country perspective, reducing the differential delays for globally important molecules will enable a more equitable access to new and possibly more effective treatment alternatives.

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and Risk Sharing Agreements introduced in the 2009 PPRS will further emphasize value-for-money in NHS purchases of medicinal products. In Germany reimbursement regulation through reference pricing includes patented pharmaceuticals in reference groups unless novelty and therapeutic improvement is demonstrated and companies take this into consideration when setting prices.

CHAPTER 3

3 Price regulation and speed of adoption of pharmaceutical innovation: evidence from the main OECD markets (1999-2008)

3.1 INTRODUCTION

The pharmaceutical industry has traditionally had an international character with substantial foreign direct investment in marketing and production in order to recoup R&D costs or satisfy local clinical trial requirements. Multinational pharmaceuticals are faced with increasing challenges in developing international market strategies for new products. The first and arguably most important challenge following product registration is the international launch strategy, i.e. timing and order of market entry, which is compounded with difficulties due to the unique and often country-specific regulatory nature of the pharmaceutical industry. Pricing and reimbursement regulation is geared towards cost containment goals, along with other objectives such as promoting rational drug use, ensuring value for money and less commonly protecting national industry against international competition. While there is a small literature on the effect of regulation on drug prices and competition, the evidence regarding the impact of regulation on the launch timing of pharmaceutical innovation is scanty.

The aim of this chapter is to improve our understanding of the effects of regulation on the speed of adoption of new pharmaceutical products (adoption in this paper is specified by the first launch date of a given molecule). This chapter contributes to the literature by empirically exploring the launch timing of new molecules in different countries that make up the world innovative drug market. Drawing upon duration modelling on IMS (Intercontinental Medical Statistics) data I investigate how regulation affects the diffusion of pharmaceutical innovation across the major OECD markets and identify strategies that firms employ to dampen the effect of price and profit spillovers in an interdependent market environment. In order to identify the effect of regulation more neatly, I control for firm and molecule heterogeneity in predicting the speed of launch across markets.

The impact of regulation on entry and social efficiency has been highlighted by various economists (Djankov, La Porta et al. 2002). Several studies have addressed how regulation affects adoption of innovation in different industries, including the domestic

construction industry (Jaffe and Stavins 1995; Dewick and Miozzo 2002), electrical utilities (Sanchez and Post 1998), the global mobile telecommunications market (Gruber and Verboven 2001), chlorine manufacturing (Snyder, Miller et al. 2003), information technology (Wallsten 2005), and agrochemicals (Sheppard, Shaw et al. 2006). The pharmaceutical industry, however, is one of the most heavily regulated industries and provides a perfect test bed to assess how regulation affects adoption of innovation across interdependent markets[49].

Pharmaceuticals deserve specific attention because consumption is channelled through an agency relationship. Accordingly, besides regulation other characteristics of the agency relationship will appear to influence the speed of adoption. Reimbursement is carried out by third party payers, which limits financial responsibility on the demand side leading to price insensitivity and moral hazard in consumption. The industry significantly depends on monopoly rights granted by patents to recoup costly R&D outlays and maintain sustainability of future investments[50]. Such monopolistic power, however, allows pricing above marginal costs, which has historically focused regulators' attention on pharmaceutical prices as a major means of cost-containment.

Governments are faced with the challenge of protecting the general population health, ensure access to safe and effective medicines, constrain rising pharmaceutical expenditures and provide incentives to stimulate pharmaceutical R&D. Regulation of the pharmaceutical sector is used as a tool to correct market failures and balance conflicting public health and industrial policy goals (Mossialos, Walley et al. 2004b). Hence, regulation in each country is the result of solving this trade off.

New pharmaceuticals tend to be products that contain global public good characteristics, as they are part of health care treatments that apply across the globe. Access to essential medicines is also increasingly recognized as a core part of the international right to health (Thomas 2006). Patents confer temporary market power to single multinational corporations as a mechanism to reimburse the costly research and development process.

[49] Regulation in the pharmaceutical sector can be targeted at either the demand or supply side, or both. Supply-side measures affect pharmaceutical prices directly or indirectly and therefore target the pharmaceutical manufacturers. Demand-side controls, on the other hand, are directed at physicians, pharmacists or patients and aim to control volume through financial and non-financial incentives (Mossialos and Oliver 2005). Supply-side controls have been the most pervasive and controversial type of control among the OECD markets.

[50] R&D investments are estimated to be on the order of $800 million, with a range of $500 million to $2,000 million depending on the therapy or the developing firm (DiMasi 2002; DiMasi, Hansen et al. 2003; Adams and Brantner 2006).

Due to this monopolistic power, pharmaceutical prices have become the main focus of insurers and regulators as a means of cost-containment. The monopoly rights offered by patents create incentives for innovation; however, such power allows firms to set prices higher than the prices in a more competitive environment. The quantity and quality of pharmaceutical innovation significantly depends on the monopoly rights to recoup the risky R&D investments, which are estimated to be on the order of $800 million (with a range of $500 million to $2,000 million depending on the therapy or the developing firm) (DiMasi 2002; DiMasi, Hansen et al. 2003; Adams and Brantner 2006). In addition, patents help to insulate firms against the risk of easy and cheap replication of drugs since manufacturing expenses are marginal compared to the capital requirements needed for product development[51].

Compared to other patent dependent industries, the lengthy drug development process leaves a short period of patent exclusivity free from generic competition[52]. Given the reliance of the pharmaceutical industry on returns to R&D investments while the product is still under patent protection, speedy and simultaneous introduction across markets would be the optimal launch strategy to maximize commercial success. However, different regulatory hurdles for pricing and reimbursement after market authorization and the dependence of prices across markets may hamper the speed of introduction of pharmaceutical innovation and an equitable access across different markets. In particular, price controls have received sharp criticism for reducing the innovative activity in the sector through lower returns to R&D (Giaccotto, Santerre et al. 2005; Vernon 2005) over the lifecycle of a product and creating differentials in the adoption and diffusion of new technologies across markets (Danzon and Epstein 2005; Danzon, Wang et al. 2005; Lanjouw 2005; Kyle 2007; Kyle 2007; Danzon and Epstein 2008; Danzon and Furukawa 2008). Regulations, therefore, may result in negative implications on equitable access to health enhancing pharmaceutical technologies.

Pricing and reimbursement of pharmaceuticals in the EU is still a national competence, which results in different pharmaceutical P&R systems. The drug lag can have different components in different countries, depending on specific local regulations. Several studies in the literature have addressed delays due to the review process (Dranove and Meltzer 1994; Thomas, McAuslaine et al. 1998; Bolten and DeGregorio 2002;

[51] www.earth.columbia.edu/cgsd/documents/lehman.pdf

[52] additional extensions of exclusivity have tried to rectify this but have not totally addressed the time lost from the effective patent life

Carpenter, Chernew et al. 2003; Carpenter and Turenne 2004), while others have focused on differentials in first marketing days across countries, which could be either due to regulatory delays or pricing and reimbursement delays.

In sum, regulation measures aimed at protecting consumer safety and enhancing efficiency might be exerting some dynamic effects on the diffusion of new pharmaceutical products. This chapter will test the hypothesis that regulation has a significantly negative effect on the speed of new molecule adoption in markets that apply these regulations and investigate the ramifications of price linkages across individual markets created by external reference pricing and parallel trade. Drawing upon duration modelling applied to IMS (Intercontinental Medical Statistics) data I estimate the impact of regulation, identified by expected launch prices, on the probability of new molecule launch across the main OECD markets during 1999-2008 controlling for market structure, firm and molecule heterogeneity. I also further examine a sub-set of markets, within the EU, to assess whether firms employ strategic pricing behaviour.

This chapter aims to address some of the methodological shortcomings of previous studies. Prior few studies with IMS price and volume data used semi-parametric Cox proportional hazard (PH) model and discrete-time implementation of the PH model by complementary log-log (hereafter referred as cloglog) regression. Due to interval censored nature of the launch (failure) times in the IMS data, this chapter adopts the discrete-time failure model as the main specification and compares marginal effects the continuous-time specification with the Cox PH model. In addition, I control for drug and firm level characteristics to avoid omitted variable bias. In contrast to the approach followed by Kyle (2007), I consider only the first indication of molecules in each market as new indications face lower barriers and costs to entry both pre- and post-authorization. This approach also avoids attenuation in standard errors due to the potential correlation in errors for different indications of a given molecule-country pair. In addition, the data used encompasses a different drug mix and a more up-to-date analysis period compared to previous studies.

The rest of the chapter is structured as follows: Section 3.2 discusses the evidence from the literature and sets the theoretical framework; Section 3.3 describes the methods; Section 3.4 presents the estimation results and finally Section 3.5 discusses the findings and policy implications.

3.2 MARKET BARRIERS TO ADOPTION OF PHARMACEUTICAL INNOVATION: EVIDENCE FROM THE LITERATURE

The literature on international diffusion of new pharmaceutical technologies starts with discussion of the drug lag in the US during the 1970s following the regulatory amendments after the Thalidomide disaster. More recently, however, the literature has shifted its focus to the drug lag in markets subject to pricing and reimbursement controls (particularly within the EU). These control measures affect the local commercial demand factors and increase the interdependency between international markets due to spillovers from application of reference pricing and the profit implications of parallel exports. Also, these markets tend to be the most significant pharmaceutical markets in terms of their share in the global sales.

Both the early and the more recent empirical literature investigate similar issues, in particular the impact of market characteristics (market size, wealth, IP protection, competition, regulation), drug attributes (therapeutic importance), firm characteristics, stringency of regulation and the national origin of pharmaceutical products on the launch differentials in local markets following the first global launch date[53]. Appendix C.1 reviews the earlier, technically less sophisticated literature as well as the evidence regarding review times in the US and EU. Basic findings of the earlier literature are as follows:

- The term "drug lag" was coined by Wardell in 1970s to raise awareness of the unavailability of new drugs in the US following the 1962 Drug Efficacy Amendments (Wardell 1973; Wardell 1974; Wardell 1978).
- Besides regulation, the impact of market size, price levels, and ease of marketing are also considered as influential factors on mean lags per country and the number of new products launched in each country (Cullen 1983; Parker 1984).
- The drug set selected for multi-country analysis has a significant effect on mean delays in adoption. There is a direct relationship between the therapeutic contribution of a new drug and its likelihood of achieving widespread introduction (Parker 1984; Barral 1985; Coppinger, Peck et al. 1989).
- Stringency of the drug regulatory systems emerges as an important determinant of drug delays in the early literature (Andersson 1992; LaFrancis Popper and Nason 1994).

[53] Global launch indicates the first launch among the countries within the analysis

- Product and firm attributes (therapeutic importance and scale economies) may have an affect on the review times (Dranove and Meltzer 1994; Carpenter and Turenne 2004).
- Several studies investigate the impact of different legislative acts in 1970s-1990s on drug availability and adoption across multiple countries (LaFrancis Popper and Nason 1994; Reichert 2003). Overall, legislations that encourage the development of innovative products reduce clinical development and approval times.

The following section reports on the later literature that is more relevant to the analysis undertaken in this chapter.

3.2.1 Price Controls as a Market Barrier to Entry

Following the changes in the regulatory and commercial landscape of the pharmaceutical market throughout the 1990's, a body of literature examining the impact of price controls on the extent of launch and launch delays of new pharmaceutical products across different countries has emerged. An overwhelming majority of these papers, however, focus on developed markets. These studies can be broadly categorized into two with respect to the way regulation is identified. The first category uses proxy measures for regulation (such as dummies for price control) at the time of first global launch that are rough and may be inaccurate since regulation is multidimensional and complex (Lanjouw 2005; Heuer, Mejer et al. 2007; Kyle 2007). In addition, dummies exhibit multi-collinearity with the country effects. The second category incorporates product-specific data on actual prices to account for the impact of regulation (Danzon and Epstein 2005; Danzon, Wang et al. 2005; Danzon and Epstein 2008). Incorporating price information provides more insight into the net effect of regulation since price levels provide more variation over time, across products, firms and countries.

3.2.1.1 Identification of Regulation

Treatment dummies for some or extensive price control

Lanjouw (2005) investigates how policy choices regarding patent rights and price regulation affect decision and speed of launch by using IMS data for the launch of 836 new drugs in countries across all income levels over the period 1982-2002. Stringency of price control is measured by dummies indicating some or extensive price control. The analysis is carried out separately for high-income and low-middle income countries. For high-income countries, models are estimated on a high-quality subset of NCE's[54] whereas for the low-middle income group the focus is on blockbuster drugs[55]. The models account for local technical capacity (country R&D expenditure in all areas as a share of GDP) and strength of patent protection (availability of product and process patents, and patent rights restriction on a 0-1 scale).

According to Lanjouw's findings lower income countries have fewer drugs launched and longer delays[56]. Long term product patents do not increase drug availability in lower income countries. Short-term IP (4 years for product patents) or long term process protection only shortens launch delays in the developing world. In developing countries, price regulation does not prevent products from entry but influences timing, although moderate price regulation has no impact on timing.

In high-income countries both extensive and moderate regulation negatively impact extent of market entry; and extensive control damages the likelihood of a quick launch. Essential drug lists reduce market entry and national formularies are associated with less rapid entry. The probability that blockbuster drugs are launched within two years is considerably higher (Lanjouw 2005).

Treatment dummies for direct or indirect price controls

Other studies control for direct price controls (international price comparisons, therapeutic value/cost-effectiveness, pharmaceutical contribution to the economy) and indirect price controls (profit control, reference pricing) to test how different price and reimbursement regulation schemes affect the probability of early launch (launch within 8 months of first global launch). For example, Heuer, Mejer et al. (2007) analyze the

[54] NCE's launched in the US or UK within 2 years of marketing approval

[55] A blockbuster drug is a drug generating more than $1 billion of revenue each year

[56] Parker 1984 observes a similar result

launch delay of new chemical entities approved by the EMEA's centralized procedure between 1995 and 2004 (Heuer, Mejer et al. 2007). This approach isolates the impact of market authorization regulations. The study uses IMS Drug Launches database to analyze the launch experience of NCEs within the former EU15 in the outpatient (retail) sector during 1995-2005. A probit model, where success is defined as launch within 8 months of market authorization approval, is estimated.

The basic finding of the study is that countries with the highest probability of launch impose the lowest regulation on prices. The use of international price comparisons has a significant negative impact on the timing of new drug launches. Indirect price controls do not turn out to be a significant factor to explain launch delays, at least for on-patent drugs. The main shortcoming of this analysis is the loss of time information since the probit model does not make use of duration data and only distinguishes between launches within 8 months of approval and those that took longer than 8 months. This study does not control for drug and firm level heterogeneity, and ex-ante price and profit expectations are not considered.

Treatment dummies for different types of price controls and price ranks

Another stream in the literature uses price ranks to account for different price levels in addition to including regulation dummies, (e.g. control measures for prescription budgets, reference pricing, the use of pharmacoeconomic evidence, and price freezes and controls) (Kyle 2007). Kyle (2007) finds evidence of the spillover of regulatory controls to other international markets in her analysis of new drug launches in 28 countries (21 of which belong to the OECD) over 1980-2000. Launches are modelled as a function of competition, market (country-therapeutic class-year triple), firm and drug characteristics. Price controls affect entry decisions not only in the country that imposes them but in potential markets as well. Launch in a price-controlled country reduces the likelihood of introducing products in additional markets whereas launch in a high-priced market has the opposite effect. Methods used by Kyle (2007) include a negative binomial model to analyze the number of countries in which the drug is marketed, and a discrete-time hazard model to assess whether price controls delay launch, both of which use time to launch data.

An important contribution of Kyle (2007) has been to investigate the impacts of competition (non-generic), firm and molecule effects on launch in addition to

controlling for regulation[57]. Competition, firm and drug effects are identified as significant factors that explain differentials in launch (Kyle 2006; Kyle 2007). The existence of competing drugs is associated with an increased rate of entry. Speed of launch increases with drug importance (proxied by the share of Medline citations) and the number of other markets the drug has entered. Extensive international and local firm experiences shorten launch delays. Firms with many drugs in their portfolios tend to launch their drugs in fewer countries, which according to Kyle indicates firm efforts to match a market to the most appropriate treatments. No evidence is found regarding the negative effect of demand-side controls on launch.

Criticisms applied to Kyle (2007) may be directed to the definition of a new drug. Each new indication for a given molecule is treated as a new drug. However, new indications do not face the same barriers of entry as the first indication since price negotiations may be simpler and clinical trial requirements less for new indications. In addition, different indications for a given molecule-country pair would have correlated errors which could result in attenuation of the standard errors of the coefficients. Another issue is the static nature of the price ranks. In reality, price ranks may be heterogeneous with respect to the therapeutic subgroup or across time.

Prices as a Proxy of Regulation

There is a growing body of literature suggesting that mechanisms such as parallel trade and external reference pricing that create interdependencies in price and profits have increased launch delays and decreased the extent of launch in low-priced countries. The effects of these spillovers effects on the launch delay of new drugs have been studied by Danzon and Wang (2005), Danzon and Epstein (2005), Danzon and Epstein (2008) by using different sets of drugs and different time periods. A common measure of launch delays in all these analyses is the difference between the global launch date and country-specific launch date. Therefore, it is not possible to distinguish between finer delays due to market authorization and P&R approval. Danzon and Wang (2005) use a Cox proportional hazard model whereas the remaining papers adopt a discrete time

[57] Control variables include the number of potential competitors (number of molecules that have launched in other markets), corruption and market competition indexes (entry costs as percentage of GDP per capita), firm-level variables such as the number of countries in which the firm has launched any drug; number of drugs marketed by the firm in the country of launch and portfolio size; drug-level variables such as drug age, the number of countries in which the drug has been introduced, and the share of Medline citations

implementation of the proportional hazard model with complementary log log regression.

Expected price: Lagged average competitor price per SU prior to global launch

Danzon and Wang (2005) analyze the launch of 85 NCE's in 25 markets, including 14 EU countries, by using IMS price and volume data over 1994-1998 presented in annual quarters. Controlling for market size[58] and per capita income, the effects of expected price on launch probability and launch delay are analyzed. Expected price is proxied by the lagged average price per standard unit [59] (SU) for the therapeutic class (ATC3) in quarters 3 and 4 prior to the first global launch. Expected market size is proxied by sales in SUs in the therapeutic class in the two quarters prior to the first global launch date. Control variables include the firm's worldwide sales at the beginning of the study period, domestic launch, therapeutic category (ATC1 code), GDP per capita and country indicators relative to the UK. Estimates indicate that the hazard of launch is positively related to expected price, expected sales volume, home country and worldwide sales of the firm. Extent of launch is highest for markets with uncontrolled prices (US, Germany and the UK) whereas lower priced countries have both fewer launches and longer launch lags. Major parallel export EU countries have longer launch delays controlling for expected price and volume.

Danzon, Wang et al. (2005) use the expected price and volume before the global launch date; the impact of the change in prices and volumes over time after the global launch is not accounted for. A limitation of this study is that it does not identify the effect of time-varying factors such as age of the new chemical entity (NCE), the change in the market structure and the competitive landscape of the therapeutic subgroup. The Cox proportional model implicitly assumes that there is an average and linear price effect in the hazard that is valid for every NCE; interactions of time and price are not modelled. In addition, incorporation of generic prices in the calculation of expected prices may underestimate the expected price in countries with loose price regulation and strong generic penetration (US, UK, Germany) and result in imprecise coefficient estimates.

[58] Sales in standard units in the therapeutic class in the two quarters prior to the first global launch date

59 IMS standard unit is defined as the smallest dose for each product form, for example, one tablet, one capsule, 5 ml of liquid

Expected price: Lagged average competitor price per SU prior to local launch

The other two main papers utilizing price information are by Danzon and Epstein (2005, 2008). These papers estimate a discrete-time implementation of the proportional hazard model to identify the effects of price and competition on launch timing decisions (Danzon and Epstein 2005; Danzon and Epstein 2008). In addition, prices at which new drugs are launched are estimated by OLS regression. Average lagged competitor prices in the therapeutic subclasses are used to measure the net effect of regulation. The papers differ by the number of therapeutic classes and the analysis period. Danzon and Epstein (2008) analyze launch experience in 15 countries[60] for drugs in 12 therapeutic classes[61] over the decade 1992-2003, whereas the 2005 paper covers the sales of drugs from 4 therapeutic classes[62] in 9 countries[63] during 1990-2001. Products are categorized into new (superior) and old (inferior) subclasses which provides a pseudo classification of innovation. However, the exact definitions of what constitutes "old" and/or "new" is not clearly reported[64]. It is suggested that most superior molecules are potentially global molecules that can meet the safety and efficacy standards of all the major regulatory agencies, whereas the inferior classes may include molecules with different mechanisms of action, some of which might not meet the more stringent regulatory standards of the US FDA or the EMEA (Danzon and Epstein 2005). Such a division, as authors claim, aims to investigate the dynamic (between subclasses) vs. static (within subclass) competition in the pharmaceutical industry by carrying out separate analyses of launch experience in new vs. old subclasses.

Danzon and Epstein (2005) estimate the launch hazard equation by using baseline price levels of branded and generic competitors prior to global launch, baseline market size of the therapeutic class, and the changes in these covariates for superior and inferior molecules from baseline to time *t*. Danzon and Epstein (2008), on the other hand, consider only lagged average price and volume in SUs of competitor brand products in

[60] UK, Netherlands, Sweden, Germany, France, Greece, Italy, Portugal, Spain, Canada, Japan, Switzerland, USA, Brazil, and Mexico

[61] Anti-asthmatics, anti-clotting, anti-depressants, epileptics, anti-nauseants, parkinsons, anti-psychotics, anti-ulcerants, lipid lowering, migraine, osteoporosis, anti-hypertensives

[62] Anti-depressants (tricyclics, SSRI, SNRI), anti-ulcerants (H2 antagonists, PPIs), anti-hyperlipidemics (statins), anti-rheumatics (NSAIDs, COXII)

[63] UK, Netherlands, Sweden, Germany, France, Italy, Spain, USA, Belgium

[64] Old age dummies in the regression model represent molecules that launched before 1990

the therapeutic class. The cloglog model investigates the effects of competition, market attractiveness, firm characteristics, and spillover potentials[65].

Differential Impact of Prices on Old vs. New Molecules

There exists robust evidence that the higher the expected price, the higher is the hazard of launch. However, the impact of price depends on whether the subclass is new (superior) or old (inferior). Launch hazards of superior products are significantly and positively related to the mean prices of competitor brand products in the subclass. For inferior subclass, however, the effect is not significant (Danzon and Epstein 2008). Danzon and Epstein (2005) find that it is the baseline average competitor prices that affect the launch hazard in inferior subclasses whereas for superior products launch hazard increases with the increase in prices from global launch.

To summarize, a reduction in drug prices as a result of price regulation may contribute to launch delay in the home country, while low-price countries referenced by high-price countries in the EU may suffer welfare losses. Surprisingly, sales volume of the therapeutic class, i.e. potential market size, is not a significant determinant of launch. This might be due to the fact that the volume effect is captured by prices since prices for compounds with large potential sales are set more stringently. However, this is not the case for free priced markets and the a priori expectation is that the higher the potential market size the higher the hazard of launch, at least in free or high-priced markets.

Impact of Generic Competition

There exists contradictory evidence regarding the impact of generic competition in the therapeutic category on the timing of launch. Danzon and Epstein (2008) observe that generic substitutes are not a significant deterrent to the launch of new brand products and that generic prices have no significant effect on launch prices of new superior brands which implies weak price competition between new brands and old generics. According to Danzon and Epstein (2005), however, firms delay launching innovative products in countries with generic competition and receive lower launch prices if generic competition is present in the therapeutic subclass.

[65] Spillover effects are measured by a dummy that controls for parallel import shares in the therapeutic subclass and three count variables: the number of countries a molecule has launched in low-price EU countries, high-price EU countries and high-price non-EU countries. These variables are in addition interacted with whether the potential launch is in low- vs. high-price EU country. Competition is measured by the number of generic manufacturers in superior and inferior subclasses and the number of molecules in superior and inferior subclasses

Impact of Domestic Launch on Timing of Launch

Many studies find significant evidence that local launch increases the speed of launch. Danzon and Epstein (2008) claim that local launch is faster only in certain regulated markets such as France, Italy, Spain and Switzerland and Japan (Danzon and Epstein 2008), which have strong pharmaceutical industries and industrial policies to support the local industry.

Impact of Centralized Authorization in the EU on Timing of Launch

The evidence on how EMEA affected adoption speed is not robust. Danzon and Epstein (2005, 2008) use an indicator for molecules launched since 1996 to test for the effects of the EMEA regime, which is expected to be positive if the cost-reducing effects of the EMEA outweigh the increased risk of spillovers. They find that the impact of the EMEA process is dependent on the innovativeness of the molecules: the likelihood that new drugs would be widely diffused increased for superior products whereas inferior products that were first launched after 1996 were less likely to diffuse widely (Danzon and Epstein 2005). In the 2008 paper, the impact of the EMEA regime is insignificant for superior drugs.

The tentative outcome of these two papers is that the EMEA has not affected the speed of diffusion, which contradicts my findings in Chapter 2. Several studies have shown that EMEA centralized procedure reduced approval times making mean approval times for the EMEA and the FDA comparable (Healy and Kaitin 1999; Faden and Kaitin 2008). According to Faden and Kaitin (2008), mean approval times for products approved by both the EMEA and the FDA were similar (15.8 versus 15.7 months respectively) during 2000- 2005. However, greater variability in FDA approval times is observed. Among 71 products that were approved both by the FDA and the EMEA, nearly three times as many were approved first in the United States (Faden and Kaitin 2008).

Central community authorization reduced the variation in launch delays across the EU, however, it has not eradicated the differentials in timing of launch across the member states. For centrally approved molecules Danzon (2005) observes that there is great variation across the member states both in terms of the number of markets the molecules reach and the timing of launch (Danzon, Wang et al. 2005). Chapter 2 confirmed that although centralized approval reduced variation in delays, it has not

eradicated them. However, it remains unknown to what extent price regulation explains delays vsersus firm strategies to avoid profit spillovers across markets.

The evidence regarding the impact of parallel imports on timing of launch is weak. The presence of parallel imports is found not to be associated with decreased launch hazard in the importing country. Similarly, the presence of parallel imports does not affect launch prices of superior molecules but decreases launch prices of older inferior molecules (Danzon and Epstein 2008).

3.2.2 Firm Strategies as Insider Market Barriers

Section 3.2.1 outlined the existing evidence regarding the impact of price controls as a market barrier to entry due to regulation. There is also preliminary evidence that launch delays are partly due to strategic behaviour and not just bureaucratic lag. Manufacturers may delay launch in low-price markets to avoid undermining higher prices in other countries. Spillover effects are observed to be greatest from high-price EU to low-price EU countries. Prior launch in a high-price country (Germany, the UK, the Netherlands, and Sweden) increases the probability of launch in a lower-price country (Spain, Italy, France and Belgium). Prior launch in a high-price EU country has a greater impact on the launch hazard in a low-price EU country than prior launch in another low-price EU country. Similarly, launch in a low-price EU country has a higher impact on launch in a high-price EU country than prior launch in a high-price non-EU country (Danzon and Epstein 2008). This suggests that firm strategies can impose welfare losses, particularly those of the lower-price countries.

Kyle (2007) provides further evidence that prior launch in a low-priced country reduces the number of markets the drug is launched in. However, Danzon and Epstein (2005) find no significant effect of prior launch in a low-priced EU country on next launches, and they posit that launch in low price countries is strategically timed so that it does not affect launches in other countries.

Launch price is negatively related to launch delay for innovative products (Danzon and Epstein 2005). This suggests that delay is not a bargaining strategy pursued to obtain a higher price for superior drugs but represents firm's acceptance of a low price only once higher prices have been established for the drug in other countries. In contrast, inferior drugs have a positive association between launch delay and price, which suggests that the delay for these molecules is a result of a bargaining strategy.

Full account of the literature is now given. The next section highlights basic findings and gaps in the literature.

3.2.3 Basic Findings and Gaps in the Launch Delay Literature

Table 3.1 Basic Findings from the Literature on Delays in New Drug Entry

Factor	*Effect*	*Reference*
Stringency of regulation/ Price controls	Stringency of regulation, in particular price controls, negatively affect the timing and occurrence of launch.	Andersson 1992; LaFrancis Popper and Nason 1994; Parker 1984; Lanjouw 2005; Danzon, Wang et al. 2005; Danzon and Epstein 2008
	Products of firms headquartered in a price-controlled market reach fewer markets.	
	Launch in a price-controlled market reduces probability of launch in additional markets.	
Expected price	Expected price levels are in general significantly and positively related to launch prices; lower expected prices result in fewer products and longer launch delays.	Danzon, Wang et al. 2005; Danzon and Epstein 2008
Expected market size	Although some studies find that markets with larger populations have shorter delays, there is no robust evidence that confirms the significance of expected volume in units.	Cullen 1983; Parker 1984; Danzon, Wang et al. 2005; Danzon and Epstein 2008;
Price spillovers	Price spillovers due to reference pricing and parallel trade negatively affect launch by creating incentives for firms to delay or not launch in low-priced countries.	Danzon and Epstein 2008; Kyle 2007
Competition	Existence of competing drugs increases the rate of entry	Kyle 2007
Drug importance	Important drugs diffuse widely and at a higher speed	Parker 1984; Barral 1985; Coppinger, Peck et al. 1989
Firm effects	There exist significant firm effects. Multi-nationality of firms and worldwide outpatient sales reduce launch delays	Carpenter and Turenne 2004; Kyle 2007
Domestic Launch	Drugs of domestic firms are approved earlier than foreign firms. However, Danzon and Epstein (2008) observe that this is only the case in countries where the pharmaceutical industry plays a key role in the local economy.	Parker 1984; Danzon, Wang et al 2005; Danzon and Epstein 2008

3.2.3.1 Gaps in the Literature

Early attempts to determine the nature of the relationship between the time lag and the influential factors tend to use average delays, and Pearson correlation coefficients/first order partial correlation tests (Wardell 1978; Cullen 1983). The more recent literature has used more sophisticated methods such as binary response models (probit) by defining a threshold period such that launch before that threshold is defined as success and launch after the threshold or non-launch is defined as failure. The main drawback of these analyses is the loss of time information as the actual duration data is not used. Methodologically the most powerful analyses have adopted multivariate duration analysis methods that incorporate more detailed time information.

Danzon, Wang et al. (2005) adopted the Cox proportional hazards model, which essentially assumes continuity of the failure times and relies on the proportional hazards assumption with respect to different subjects. The plausibility of this assumption has not been investigated by the inclusion of time interactions or other statistical tests. Danzon, Wang et al. (2005) include country indicators and ATC1 indicators and cluster errors at the molecule level, and do not control for firm heterogeneity. The empirical analysis in this chapter improves the specification by accounting for firm-level heterogeneity and clustering the standard errors by molecule-country. Molecule-country pairs define the subjects under risk with potential autocorrelation between errors of the same pair over time. Also, macro-trends are captured by including calendar year dummies which are not considered by Danzon, Wang et al. (2005)

Studies in the launch delay literature have been criticized for the definition of the molecule set. Garattini and Ghislandi (2007) suggest introducing the distinction between innovative and me-too drugs ex-ante in order to control for NCE heterogeneity (Garattini and Ghislandi 2007). Danzon and Epstein (2005, 2008) account for this heterogeneity by defining superior and inferior therapeutic subclasses based on how old the given subclass is. However, this seems to be a subjective time-based evaluation. A few studies use prior launch in the US or UK as an indication of global importance. This assumption can be tested by choosing molecules that have launched not only in the US or the UK but in more countries. Regressions in this study will consider prior launch in at least the average number of markets a molecule reaches (i.e. launch in more than 10 markets). This will provide the opportunity to test the impact of regulation on a more global set of drugs, which is the main interest from a policy perspective.

The market structure has so far been analyzed in terms of the number of competitor molecules. Concentration within the therapeutic subcategory has not been considered. This chapter will therefore also investigate the impact of therapeutic category concentration as a barrier of entry, in addition to the number of competitor molecules.

So far, only three studies have investigated the impact of volume in standard units on the hazard of launch. Given the same expected price, the higher the expected volume, the shorter should be the delay. However, main empirical evidence from Danzon and Epstein (2005, 2008) indicates that volume (in SUs) is not a statistically significant factor for timing of launch. This evidence dates back to 1992-2003. This chapter will provide further evidence on a more recent database that includes sales and price information during 1999-2008.

None of the studies isolate the delays due to authorization from the delays due to price/reimbursement delay which could be due to administrative reasons or due to the bargaining process. The main reason is the difficulty in obtaining such data. Delays due to authorization have been isolated for a subset of molecules that were approved through the centralized EMEA procedure.

Taking the price of competitor drugs already in the market as a proxy for expected price essentially assumes exogeneity of prices, i.e. countries commit to these prices ex-ante before the firms have decided timing of launches. However, prices might potentially be endogenous if they are correlated with an omitted variable. Similarly, entry by competitors (number of competing molecules) is taken to be exogenous. It is possible that this variable is also endogenous because factors speeding the launch of one molecule may induce entry of other potential competitor molecules.

Most importantly, no empirical research so far draws conclusions about the effect of price controls/regulation on total social welfare. The costs associated with delays to market or reduction in incentives for R&D can be outweighed by increased affordability of pharmaceuticals due to lower drug prices. In addition, the impact on total social welfare depends on the extent to which cost-effective technologies are delayed. However, no analysis so far considers cost-effectiveness criteria in assessing the launch delays.

This chapter aims to address some of the gaps in the literature. First, the set of molecules used in the regressions will be of higher global importance; therefore, the

conclusions will have more relevant policy implications. Second, a more recent time period and a more comprehensive molecule set will be considered to investigate if there are any different dynamics in the factors that determine launch hazards. Third, this analysis aims to combine findings from the economic literature with strategy and marketing literature that emphasize the significance of firm and product heterogeneity in international product rollouts. Expected prices will be used as a proxy for regulation instead of using dummies or price ranks, which will enable better control for the impact of regulation. The panel nature of the data will allow exploiting the variation in prices, i.e. regulation, and country, firm and molecule effects over time. Efficiency of the estimates will be improved by clustering errors at the molecule-country level. Robustness of the impact of regulation will be assessed by comparing outcomes for different specifications as well as including other control variables such as firm, molecule and market structure effects which have been established as influential determinants in industrial organization market entry literature.

3.2.3.2 Research Questions

The main question in this chapter is:

- How do expected prices of new molecules affect adoption of new pharmaceutical technologies?

Controlling for expected prices, additional questions that this chapter aims to address are:

- How do market size and competition in the therapeutic subgroup affect the timing of molecule launch?
- What is the impact of firm and molecule characteristics on the adoption of new pharmaceuticals?
- Is there any evidence of strategic firm behaviour to avoid the knock-on effects of price divergence in an interdependent market environment?

Detailed hypotheses tested empirically are presented in Section 3.3.4.

3.3 METHODS

A semi-parametric Cox proportional hazard model and a discrete time proportional hazard model are used to estimate the hazard of launch for molecule-country launches relative to the first global launch date (see Appendix B.3 and Appendix C.2 for technical details of the Cox model and discrete time survival analysis with *cloglog* regression). For the Cox proportional hazard model, the launch hazard of molecule j in country k at time t is defined as:

$$h_{jk}(t) = h_0(t)\exp\{\mathbf{z}_{jk}(t)\boldsymbol{\beta}\},$$

where $h_0(t)$ is the non-negative, unspecified hazard function which is common across different subjects. $\mathbf{z}_{jk}(t) = \left(z_{1jk}(t), z_{2jk}(t), ..., z_{pjk}(t)\right)$ are the covariates for molecule j - country k pair, and $\boldsymbol{\beta}$ is a $p \times 1$ vector $\left[\boldsymbol{\beta}' = \left(\beta_1, \beta_2, ..., \beta_p\right)\right]$ of unknown parameters to be estimated.

The Cox PH model assumes continuous failure times. Sometimes data summarizing spell lengths (duration from risk onset till failure) are grouped although the underlying process occurs in continuous time. Under such grouping discrete-time specifications are used. The key issue in choosing continuous versus discrete specification is the relative lengths of the intervals used for grouping the data and the typical spell length. The smaller the ratio of the interval used for grouping the data to the typical spell length, the closer is the approximation provided by the continuous time specification. The median failure time for launches after 1993 in the sample used is 14 months (the restricted mean is 30 months). Since it is not well defined how small the monthly grouping is with respect to the typical launch time, complementary log-log (cloglog) specifications are estimated for comparison. Estimation of the hazard of launch predominantly adopts the discrete-time implementation in the few papers that have emerged recently, mainly due to the grouping in the launch dates. In the cloglog model, the interval hazard rate for the launch of molecule j in country k, assuming quadratic duration dependence, is defined as:

$$h_{jk}(t) = 1 - \exp(-\exp(\gamma_t + \mathbf{z}_{jk}(t)\boldsymbol{\beta})) = 1 - \exp(-\exp(\gamma_1 t + \gamma_2 t^2 + \mathbf{z}_{jk}(t)\boldsymbol{\beta})) \text{ or}$$

$$\log\left(-\log\{1 - h(t)\}\right) = \gamma_1 t + \gamma_2 t^2 + \mathbf{z}_{jk}(t)\boldsymbol{\beta}\ ^{66},$$

[66] log(-log(.)) transformation is known as the complementary log-log (cloglog) transform

where γ_t is the pattern of duration dependence in the interval hazard[67] and $\boldsymbol{\beta}$ is the vector of regression coefficients for remaining covariates. The $\boldsymbol{\beta}$ coefficients are the same ones as those characterizing the continuous time hazard rate $h_{jk}(t) = h_0(t)\exp\{\mathbf{z}_{jk}(t)\boldsymbol{\beta}\}$. Different restrictions can be imposed on the pattern of duration dependence γ_t to identify the precise pattern of duration dependence in the continuous time. A semi-parametric form can be assumed for γ_t by including dummies for each month, quarter or year following onset of risk (see Appendix B.4 for additional information about discrete time duration analysis).

Duration dependence in the main regressions is assumed to be a second order polynomial in time. This specification was chosen empirically over a linear duration dependence in time and is line with the assumption by Danzon and Epstein (2005, 2008). In addition, semi-parametric estimation is carried out by including year dummies following global launch, which essentially assumes a constant hazard during each year following global launch.

3.3.1 Data

The Intercontinental Medical Statistics (IMS) data used in this study was collected at Merck Sharp and Dome Limited (MSD) premises in Hoddesdon UK. Quarterly MIDAS sales data was obtained from IMS for the period 1999 Q1 – 2008 Q3. The data covers 20 countries[68] which represent the major pharmaceutical markets in the OECD (except for South Africa). The IMS database contains quarterly USD ($) sales, and sales volume in standard units (SU[69]), molecule name, IMS generic and license status classification, global and local launch dates, pharmaceutical form, therapeutic class (ATC4[70]), the

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[67] $\gamma_t = \log \int_{t-1}^{t} H_0(u)du = \log(H_0(t) - H_0(t-1))$ is the log of the difference between the integrated baseline hazards evaluated at the end and beginning of the interval

[68] The country set in alphabetical order is: Australia (AL), Austria (AU), Belgium (BE), Canada (CA), Finland (FI), France (FR), Germany (GE), Greece (GR), Italy (IT), Japan (JP), Netherlands (NE), Poland (PO), Portugal (PO), South Africa (SA), Spain (SP), Sweden (SW), Switzerland (SZ), Turkey (TR), the UK, the US

[69] SU represents the number of "standard dose" units sold and is determined by taking the number of counting units sold divided by the standard unit factor which is the smallest common dose of a product form as defined by IMS Health. For oral solid forms, the standard unit factor is one tablet or capsule whereas for syrup forms the SU factor is one teaspoon (5ml) and for injectable forms it is one ampoule or vial. SU is a useful volume measure when packs or products being compared are different in form.

[70] And hence ATC3, ATC2 and ATC1

ethical or OTC sector sales, and breakdown of sales by the distribution channel. Spain, Turkey, Belgium, Greece, Portugal, Spain, South Africa have only retail channel data[71]; for Sweden retail and hospital sales are combined. Non-US distribution channels are either hospital or retail. The US market has numerous distribution channels: retail channels (drugstores, foodstores and mail service) and non-retail channels (clinics, federal facilities, HMOs, home health care, long term care, non-federal hospitals and other miscellaneous channels).

The ex-manufacturer price level for molecules is calculated by dividing the ex-manufacturer USD sales by volume in SU[72]. The cost incurred by the end-purchaser will depend on the marketing discounts, volume of purchase, and distribution margins. The analysis in this study uses ex-manufacturer retail prices since these are the prices that regulation affects; hospital prices are mostly determined on a tender-based procedure[73].

Supplementary data was obtained from online resources. OECD statistical extracts[74] were used to get additional data for country populations, percentage of population above the age of 65, life expectancy, and GDP per capita. Based on findings from the literature, these confounders were chosen to control for potential market size and different demand structures among markets. Acemoglu and Linn (2004) explore new drug introduction as a response to predictable demand increases due to demographics. They find a large effect of potential market size on the entry of new molecular entities and nongeneric drugs (1% increase in potential market size leads approximately to a 4% growth in the entry of new nongeneric drugs and new molecular entities) (Acemoglu and Linn 2004). Similarly, it has been estimated that population aging may increase drug expenditures by 1 to 3 % per year making market entry for new drugs more attractive (Van Tielen, Genaert et al. 1998; Merlis 2000; Gerdtham and Lundin 2004). In addition, GDP per capita controls for variations in willingness to pay levels in different markets. Sales data were deflated using GDP deflators obtained from the International Monetary Fund World Economic Outlook Database 2008. Finally, Corruption Perception Index scores were downloaded from the website of Transparency

[71] Launch in these countries therefore represents launch in the retail sector.

[72] In this study, only ex-manufacturer price levels are considered and regulation along the distribution chain is ignored

[73] The average price level during a quarter is assumed for each month in a given quarter.

[74] Available at http://stats.oecd.org/index.aspx

International, a global civil society organisation leading the fight against corruption[75] (supplementary data is presented in Appendix C.4).

The analysis is carried out at the molecule level. Molecules in the IMS data are characterized by the Anatomic Therapeutic Classification (ATC) system (see Appendix A.1 for the description of the ATC system). The literature has used 3-digit ATC (Pharmacological subgroup) and 4-digit ATC (Chemical subgroup) as a proxy for a given product's potential market. This study uses ATC4 as the potential market to calculate expected price and volume since immediate competition between molecules occurs at the ATC4 level. Although some studies consider additional indications as a separate market (Kyle 2007), the analysis in this study considers the first indication, i.e. the first ATC4 subgroup in which the molecule launches first. This approach is consistent with the approach followed in other papers and focuses on the launch of a given molecule for the first time when no clinical prior experience exists related to the molecule in the local market.

Observations with negative sales representing products returned to the manufacturer after withdrawal from the market, and which accounted for about 5% of the total number of observations, were dropped. This avoids bias due to inclusion of low-quality products that do not meet standards of safety and efficacy in the post-marketing phase. Sales figures in USD dollars were deflated by IMF GDP deflators for each country-year using 2000 as the base year (see Table C.23 in Appendix C.4 for GDP deflators)[76].

The global launch date of a given molecule defines the onset of risk for further launches in the remaining markets as in Chapter 2[77]. The IMS data has launch dates recorded in months and years; without loss of generality, the fifteenth of each month is assigned as the day of launch. Failure time for molecule *j*-country *k* pair is defined as the difference between the global launch date of molecule *j* and the local launch date of molecule *j* in country *k*. The molecule set in the IMS database is restricted to include (potentially) global molecules. I adopt a more stringent measure of global importance compared to studies in the literature. Prior studies at best consider either US or UK molecules whereas this study analyses molecules that launched in more than ten countries, which

[75] http://www.transparency.org

[76] Real sales figures were calculated as : Real Sales = Nominal Sales*100/GDP deflator

[77] If the local launch date is not available in the IMS data for launches after 1999, the first sales period is assigned as the local launch date. Missing global dates are proxied by the minimum launch date in the 20 markets.

corresponds to half of the markets in this dataset. Due to different dynamics after the establishment of a single European market in 1993, the molecule set is further restricted to account for launches that occur after 1993.

The dataset is expanded such that for each molecule-country pair there exists 117 months (from January 1999 till September 2008) which brings the dataset into a panel data format. Time intervals are defined in months since launch dates are reported in years and months.

3.3.2 Model

Entry of a molecule in a given country can be considered as a binary-outcome model defined as unity if entry occurs at time *t* and zero otherwise (Geroski and Machin 1991). Letting Π_{jkt} represent the discounted post-entry profits for molecule *j* in country *k* if entry occurs at time *t*, the entry decision d_{jkt} is defined as:

$$d_{jkt} = \begin{cases} 1 & \text{if } \Pi_{jkt} > 0 \text{ and } d_{jkn} = 0, \text{for all } n \leq t\text{-}1 \\ 0 & \text{otherwise} \end{cases}$$

Π_{jkt} is composed of the discounted future profit stream, net of any costs of entry. Π_{jkt} is a latent variable which is not observed directly; only the launch decision d_{jkt} is observed. In an isolated market, the expected discounted future profit stream at time *t* ignoring marginal costs is $\Pi_{jkt} = \sum_{l=1}^{LT_{jk}} \delta^l \{P_{jkl} \cdot Q_{jkl}\} - E_{jkt} + \nu_{jkt}$, where P is the expected local price; Q is the expected market size for molecule *j* in country *k*; E is the fixed cost of entry; LT is the expected life-time of the molecule in the destination market and δ is the discount factor. Considering the difficulty in raising prices post-entry due to regulation or competition, companies would like to launch as quickly as possible. However, in interdependent markets such as the EU, there would be an additional loss term (L) due to external referencing or parallel trade between the destination market *k* and markets *r* that have already adopted the technology and reference prices in market *k* (Danzon and Epstein 2008). The profit equation would then become

$$\Pi_{jkt} = \sum_{l=1}^{LT_{jk}} \delta^{l} \left\{ P_{jkl} \cdot Q_{jkl} - \sum_{r \neq k} L_{jkrl} \right\} - E_{jkt} + v_{jkt},$$ which shows the international character of pricing and launch strategies of new pharmaceutical products. The size of the loss L would depend on prices and market sizes in markets k and r. Companies could forego launch in small sized and low-priced markets to preserve profits in bigger markets with higher prices. The expected price P is also a function of price controls and the degree of competition in the therapeutic subgroup.

One of the key product attributes of on-patent pharmaceutical technologies is quality. A quality advantage (addressing unmet needs or offering improved effectiveness and/or fewer side effects) potentially results in a price mark-up. Even in price-controlled markets, e.g. France, where the pharmaceutical sector plays an important role in the economy, price mark-ups are given as an incentive to stimulate pharmaceutical innovation.

The expected market size Q depends on total sales in the therapeutic category, which is a function of the population and the prevalence rate of the condition as well as demand-side controls that may define limits on Q through price-volume agreements. Depending on firms economies of scale, firms can invest in promotional efforts to influence prescribing decisions of physicians to increase the volume of sales.

Let $\mathbf{R}, \mathbf{C}, \mathbf{M}$, and $\mathbf{F}$ be row vectors of regulation, market size and competition, molecule, and firm characteristics respectively. Vector $\mathbf{R}$ includes price P, cost of entry E, and the size of the loss L. Market size and competition vector $\mathbf{C}$ includes expected market size Q and market structure variables such as number of firms and concentration index. Vector $\mathbf{M}$ captures heterogeneity in molecules; therapeutic importance affects commercial success of new molecular entities through higher price mark-ups (P) and higher global sales. Finally, vector $\mathbf{F}$ captures heteroegeneity in firms that affect firm capability on overcoming costs of entry E. The additive reduced-form profit function can be specified as:

$$\Pi_{jkt} = \mathbf{R}_{jkt}\boldsymbol{\beta}_R + \mathbf{C}_{jkt}\boldsymbol{\beta}_C + \mathbf{M}_{jk|t}\boldsymbol{\beta}_M + \mathbf{F}_{jk|t}\boldsymbol{\beta}_F + \gamma_t + u_{jkt} = \mathbf{z}_{jkt}\boldsymbol{\beta} + \gamma_t + u_{jkt},$$

where $\boldsymbol{\beta}_R$, $\boldsymbol{\beta}_C$, $\boldsymbol{\beta}_M$, and $\boldsymbol{\beta}_F$ represent corresponding column vectors of parameters to be estimated. γ_t is a function of time since global launch t of molecule j. Let $\mathbf{z}_{jk}(t)$ be a $1 \times p$ matrix defined as: $\mathbf{z}_{jkt} = \left[\mathbf{R}_{jkt}, \mathbf{C}_{jkt}, \mathbf{M}_{jkt}, \mathbf{F}_{jkt}\right]$.

Given that launch has not occurred up to time interval t, the conditional probability of launch during interval t, i.e. the interval hazard rate is:

$$\Pr\left(d_{jkt} = 1 \mid T_{jk} \geq t\right) = h_{jk}(t) = \Pr\left(\mathbf{R}_{jkt}\boldsymbol{\beta}_R + \mathbf{C}_{jkt}\boldsymbol{\beta}_C + \mathbf{M}_{jk|t}\boldsymbol{\beta}_M + \mathbf{F}_{jk|t}\boldsymbol{\beta}_F + \gamma_t + u_{jkt} > 0\right)$$

$$h_{jk}(t) = \Pr\left(\mathbf{z}_{jkt}\boldsymbol{\beta} + \gamma_t + u_{jkt} > 0\right)$$

$$h_{jk}(t) = \Pr\left(u_{jkt} > -\mathbf{z}_{jkt}\boldsymbol{\beta} - \gamma_t\right) = 1 - F\left(-\mathbf{z}_{jkt}\boldsymbol{\beta} - \gamma_t\right) = F\left(\mathbf{z}_{jkt}\boldsymbol{\beta} + \gamma_t\right)$$

,

where $F(.)$ is the cumulative distribution function of u and T_{jk} is the launch time of molecule j in country k. For the cloglog model $F(\mathbf{z}_{jkt}\boldsymbol{\beta} + \gamma_t) = 1 - \exp\left\{-\exp(\mathbf{z}_{jkt}\boldsymbol{\beta} + \gamma_t)\right\}$ and thus the hazard rate can be defined as:

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

The marginal effect of the hazard with respect to $\mathbf{z}_j$ has the same sign as the parameter estimate and is given by:

$$\frac{\partial h}{\partial z_j} = \exp\left\{-\exp\left(\mathbf{z}_j\boldsymbol{\beta} + \gamma_t\right)\right\}\exp\left(\mathbf{z}_j\boldsymbol{\beta} + \gamma_t\right)\beta_j .$$

The discrete time failure analysis assumes two different duration specifications: i) a parametric specification for $\gamma_t = \gamma_1 t + \gamma_2 t^2$; and ii) a semi-parametric specification that includes dummies for each year following global launch.

Similarly for the Cox model the hazard of launch is defined as:

$$h_{jk}(t) = h_0(t)\exp\left\{\mathbf{z}_{jkt}\boldsymbol{\beta}\right\} = h_0(t)\exp\left\{\mathbf{R}_{jkt}\boldsymbol{\beta}_R + \mathbf{C}_{jkt}\boldsymbol{\beta}_C + \mathbf{M}_{jkt}\boldsymbol{\beta}_M + \mathbf{F}_{jkt}\boldsymbol{\beta}_F\right\}$$

Given the risk set $RS(t)$ at time t defined as molecule-country pairs (i,l), the probability that molecule j launches in country k, i.e. failure of the pair (i,l), is defined in the Cox model as:

$$\Pr\left((j,k) \text{ fails} \mid RS(t)\right) = \frac{h_0(t)\exp\left(\mathbf{z}_{jkt}\boldsymbol{\beta}\right)}{\sum_{(i,l)\in RS(t)} h_0(t)\exp\left(\mathbf{z}_{ilt}\boldsymbol{\beta}\right)}$$

See Appendix C.2 for a fuller discussion of the model including definition of marginal effects and parameter interpretation.

3.3.3 Variables: Key Drivers and Market Barriers to Adoption of Pharmaceutical Innovation

I classify variables that define the decision of entry broadly as external environment and internal environment factors (see Table 3.1). External environment variables are those defined outside the boundaries of the firm, whereas internal environment variables are defined by firm strategies and internal managerial decisions. This approach brings together the conceptual framework used in the marketing and strategy literature with the findings from the industrial organization (IO) literature regarding the drivers of market entry (Chryssochoidis and Wong 1998; Wong 2002). A list of descriptive statistics for the variables is provided in Appendix C (Table C.2). External environment variables include regulation (**R**), market environment and competition (**C**), whereas internal environment is defined by variables that control for firm (**F**) and molecule heterogeneity (**M**).

3.3.3.1 External Environment

Regulatory Environment

This is the main variable of interest in this chapter. Due to the complexity and diversity of the regulatory environments in the markets under study, the impact of regulation is captured by the average competitor prices in the same therapeutic sub-group lagged by one quarter prior to local launch. Expected prices are still significant if a moving average is used for molecules launched after 1993. Short-term fluctuations in the raw price data are smoothed out by using the moving average of prices, which provides a more general picture of the underlying price trend over time. Instead of using a simple

moving average, I defined moving averages over the past four quarters by giving more weight to recent quarters, i.e. 0.4, 0.3, 0.2 and 0.1 respectively for the first, second, third and fourth lags. In Section 3.4.1.1, I investigate how the price effect changes over time by interacting lagged prices with time since global launch.

Identification of regulation by lagged prices has been adopted only by few papers that had access to price information (Danzon and Epstein 2005; Danzon, Wang et al. 2005; Danzon and Epstein 2008). In addition, several studies that investigate the relation between price regulation and R&D spending have used price as a proxy for the effects of price regulation (Giaccotto, Santerre et al. 2005; Golec and Vernon 2006). In light of the evidence from the entry literature it is expected that higher expected prices will increase the hazard of launch.

Market Environment

The second main variable of interest is the expected market size. Expected market size for a new molecule is the sales in SUs within the ATC4 category in individual markets lagged by one quarter[78]. ATC4 classes represent molecules within the same chemical subgroup and therefore account for the most immediate branded-branded competition. Although theoretically, higher market size attracts more entry, the empirical evidence regarding the impact of volume in SUs on the timing of entry is mixed. Some studies have found a significant positive effect on the probability of launch (Danzon, Wang et al. 2005), whereas others have concluded that volume is not a significant variable for superior (new) molecules but has a significant role in the timing of launch of inferior (old) molecules (Danzon and Epstein 2008). The molecule set in this study is relatively new; however, no subjective evaluation can be made regarding the superiority of the subclasses. Market environment includes other variables that define the attractiveness of the market (GDP per capita, population, age profile of the population, life expectancy) or barriers to entry (e.g. corruption as a proxy for bureaucratic delays in entry). Several studies have identified that the extent of entry is significantly positively related to GDP per capita and population.

[78] Several regressions were run by defining the market at the ATC3 level to account for cross-class effects. Results indicate that cross-class effects may be significant. However, to conserve space and to enable comparison with prior results from the literature, results for market defined at the ATC4 level are reported.

Corruption has been shown to significantly reduce foreign direct investment through its effects on firm performance. Corruption affects entry-mode decisions of firms and diminishes firm-level growth. Evidence from the management literature suggests that firms prefer short-term contracting and partnering or entry through wholly owned subsiiaries in corrupt markets (Shleifer and Vishny 1993; Rodriguez, Uhlenbruck et al. 2005; Uhlenbruck, Rodriguez et al. 2006).

This should introduce additional entry costs through extra search costs and additional bribe implications, and therefore, delay launch of new molecules. Kyle (2007) uses the corruption perception index (CPI) score provided by the Transparency International. She concludes that less corrupt markets are less attractive for quick entry. I incorporate the same CPI, which varies over the observation period. During 1999-2008, based on average scores the top 4 most corrupt markets are Turkey (3.65), Poland (3.94), Greece (4.48), Italy (5); and the top 4 least corrupt markets are Netherlands (8.85), Switzerland (8.85), Sweden (9.26), and Finland (9.64)[79]. Findings from Chapter 2 suggest that there is negative correlation between perceived corruption and the speed of innovation adoption. Incorporating the same variable as in Kyle (2007) allows testing for the impact of corruption.

Competitive Environment

Economic theory predicts that entry depends on the level of competition and market structure. The pharmaceutical industry exhibits two types of competition: branded-generic and branded-branded. Branded-generic competition is the competition that occurs between products with the same active ingredient once the patent for the originator product expires. Branded-branded competition is defined as the competition between products with different active ingredients within the same therapeutic subgroup and is proxied by the number of competitor molecules within the therapeutic subgroup. Kyle (2007) uses a similar definition and observes that higher number of competitors increases the probability of entry.

Although the extent of generic competition affects sales and market power in the later stages of the product life cycle, several studies in the literature empirically demonstrate that intermolecular competition reduces the net present value of a drug product more than due to the entry of generic competition (Stern 1996; Berndt, Bui et al. 1997;

[79] A score of 10 indicates the least corrupt market, and 0 the most corrupt

Lichtenberg and Philipson 2002). Since no chemically equivalent generics exist for molecules that are entering a market for the first time, generic competition within the ATC4 subgroup is proxied by the number of molecules with existing generic competition. Danzon and Epstein (2005, 2008) use the number of generic manufacturers per molecule lagged by one quarter, which turns out to be statistically insignificant.

No studies so far have considered the impact of molecule concentration on the hazard of launch. The number of competitors on its own does not account for how concentrated the market power is in the therapeutic subgroup. It is a stylized fact that high concentration reduces the equilibrium level of entry in several industries. This study incorporates concentration by defining the concentration index for the therapeutic subgroup based on the market share of molecules within the same ATC4, namely the Herfindahl-Hirschman Index (I_{HH}). I_{HH} is a convex function of market shares which is sensitive to unequal market shares. The concentration index of a therapeutic subgroup in each country is defined as the sum of the squares of market shares of molecules within the ATC4, i.e. $I_{HH} = \sum_{i=1}^{N}\left(s_i^{\,2}\right)$, where s_i is the market share of molecule i and N is the number of molecules in the therapeutic subgroup.

Table 3.2 Variable Definitions and Descriptive Statistics for the Data used in Survival Analysis

External Environment	**Variable Name**	**Descriptive Statistics[b]**			
Regulatory Environment		*Mean*	*Std Dev*	*Min*	*Max*
Expected Price	Log Lagged Avg Non-Generic Price/SU in Ctry-ATC4[a]	0.43	2.5	-10.161	8.16
Relative Price	High Price EU	0.29	0.46	0	1
Price Setting	External Referencing	0.83	0.37	0	1
Market Environment					
Expected Market Size	Log Lagged Total SU in Ctry-ATC4	7.03	3.27	-6.91	14.7
GDP per capita	Log GDP per capita ($)	10.13	0.39	8.99	10.74
Population	Log Population (000s)	10.08	1.03	8.55	12.62
Age profile of the population	Population > 65 yrs (000s)	6128	7765	762	38678
Health profile of the population	Life expectancy in yrs	78.61	2.73	69.5	82.8
Corruption	Corruption Perception Index	7.06	1.931	3.1	10
Competitive Environment					
Market Concentration	Log Molecule Concentration in Ctry-ATC4(IHH)	10.058	1.158	5.72	15.94
Intermolecular Competition	Log Number of Molecules in Ctry-ATC4	1.401	1.795	-4.61	5.42
Generic Competition	Number of Molecules with Generic Comp in Ctry-ATC4	0.647	2.253	-4.61	5.29
Internal Environment					
Firm Characteristics					
Economies of Scope	Log Firm Sales (global) in 2007	14.9	3.21	-4.56	17.45
	Log Number of Countries Firm has Launched in	2.45	1.03	0	3
Economies of Scale	Log Firm's Total Number of Molecules	5.49	1.47	0.00	7.22
	Log Local Firm Experience (number of molecules launched)	4.09	1.33	0	6.65
Location of Firm Headquarters	Domestic Launch	0.11	0.31	0	1
Molecule Characteristics					

Therapeutic/Commercial Importance	Log Global Molecule Sales in 2007	11.038	2.194	-4.88	16.26
	Log Molecule's Global Reach (total markets launched in)	2.713	0.211	2.3	3
Cumulative Markets Diffused at t	Log Markets Launched in at t	1.307	1.11	0	3
Period of Global Launch (old vs new)	First Launch Before 1999	0.67	0.47	0	1

Note: [a] All lags are by one quarter. [b] Descriptive Statistics are for the transformed form used in the regressions. See Table C.2 in Appendix C.3.1, for descriptive statistics of non-transformed variables.

3.3.3.2 Internal Environment

Firm Characteristics

Firm effects have been found to be significant in the strategic entry decisions within the pharmaceutical sector (Scott Morton 1999; Kyle 2006; Kyle 2007). I account for firm effects by using proxies for economies of scope and economies of scale in determining firms' timing of launch. I do not use firm fixed effects due to the large number of firms in the dataset, which prohibits estimation. Including firm dummies resulted in insufficient memory to complete the regressions runs (there are 578 different firms, which results in 622 dummies in total together with country, ATC1 and calendar year effects).

Firms with higher economies of scale have better prospects of entry through licensing in foreign markets and cost advantages compared to smaller firms to overcome costs of entry (both for the clinical trials stage and registration and price approval). Similarly, economies of scope are expected to speed international diffusion through R&D and knowledge spillovers for different drugs. The higher the number of molecules launched in a given market, the higher the familiarity of the firm with the requirements of the regulatory authority. These learning effects can enable firms to come up with more efficient launch strategies. Similarly, clinical trial data obtained in one country can generally be used for launch in further markets. Log transform of firm sales in 2007 and the number of countries the firm has launched in are used to account for economies of scale. I proxy economies of scope by the number of different molecules (active ingredients) a firm has marketed, which gives an indication of past portfolio diversity.

Numerous studies observe home-country advantage for launching firms (Danzon, Wang et al. 2005; Kyle 2006; Kyle 2007). A domestic launch is represented by firms launching in markets where their headquarters are located.

Firm attributes may have an affect on review times as well. Carpenter and Turenne (2004) observe a large-firm advantage in pharmaceutical regulation primarily due to familiarity of the regulator with large firms and regulators favouring early entrants (Carpenter and Turenne 2004).

Molecule (Product) Characteristics

Branded-branded competition in the pharmaceutical sector is based on quality rather than price. Therapeutic benefits of a new molecule define the quality and enable product differentiation due to an improved quality profile. Therapeutic importance, therefore, may result in quicker entry as firms may strategically push for a faster international rollout to obtain higher net returns. Faster launch may also occur due to regulatory reasons since therapeutic importance of molecules is the main criteria used in many countries for price setting and reimbursement decisions. Products that have a significant therapeutic advantage may be eligible for a fast track approval and may receive a price mark-up compared to already existing products.

Dranove and Meltzer (1994) provide evidence from the US suggesting that more important drugs are developed and approved more rapidly. Within the US this also translates to quicker launch since products do not have to go through pricing negotiations as in the EU. Importance is found to affect both the time from first worldwide patent application to new drug application (NDA) and time from NDA to NDA approval. However, the generalizability of the results to the EU context is limited due to the different dynamics in the EU (Dranove and Meltzer 1994).

Both the early and recent literature find evidence that therapeutically important drugs diffuse internationally quicker and to a wider set of markets. Therefore, the total number of markets in which a molecule has launched (global extent of launch) is used as a proxy for relative therapeutic importance. A second proxy is defined as molecule's global sales in 2007 since therapeutic importance and commercial success are highly positively correlated. Finally, the cumulative number of markets a molecule has launched on a yearly basis is included as a third measure. This is expected because firms optimize launch strategies for a given product jointly for different markets. The faster the molecule diffuses following global launch; the lower the probability of launch in the remaining markets.

Several other measures have been used in the literature to define therapeutic importance. FDA ratings of novelty has provided a proxy in the past for products that were approved in the US (Dranove and Meltzer 1994; Lu and Comanor 1998). Parallel to the rising importance of health technology assessment and the drive to get value for money, such evaluation is currently implicitly or explicitly being carried out by several markets in Europe as well. For instance, French authorities define therapeutic value as

the medical benefit and the improvement in medical benefit over existing products. However, such information is not publicly available for empirical testing.

3.3.4 Hypotheses

The set of hypothesises tested in this chapter are presented in Table 3.3.

Table 3.3 Hypotheses for the key drivers of adoption in the branded pharmaceutical sector

	Factor	*Testable Hypotheses*	*Evidence from the Literature*	*Expected Sign of the Coefficient*
External Environment	Regulation	H1 a.1: High expected prices increase the speed of cross-country diffusion of pharmaceutical innovation; therefore, price regulations that reduce prices result in delayed access to pharmaceutical innovation.	Exists, but limited	+ Price Coefficient (Expected due to price spillover effects, also high-priced markets usually have fewer pricing controls which allows quicker market access)
	Market	H1 b.1: Pharmaceutical innovations with a higher expected market size (sales volume in ATC4) diffuse internationally faster, controlling for the effect of expected price.	Contradictory	+ Market Size Coefficient (Controlling for expected prices, high-volume markets [in $] should have quicker launch to maximize returns on R&D and benefit from longer market exclusivity)
		H1 b.2: Corruption reduces the speed of adoption of pharmaceutical innovation	Contradictory (- in tele-communications, + in pharma-ceutical sectors)	- Corruption Coefficient (Corruption results in complicated entry mode, favours joint ventures and partnerships, increases entry costs due to time costs as well as demand for bribes, and diminishes potential firm-level growth).
	Competition	H1 c.1: A higher therapeutic subgroup concentration (molecule concentration in ATC4) reduces the hazard of launch.	No evidence	- Concentration Coefficient (According to the industrial organization literature concentration reduces the equilibrium level of entry in several industries)
		H1 c.2: Branded-branded competition is a significant determinant of the launch hazard and more important compared to the extent of generic competition in the therapeutic group.	Exists, but limited	- Branded Competition Coefficient (For new molecules the most imminent competition is branded competition. Competition drives prices down if differentiation is not strong enough and reduces incentives for entry)

Internal Environment	Firm	H1 d.1: Firm economies of scale and scope increase the hazard of launch (proxied by global firm sales and number of molecules in the portfolio)	Exists	+ Economies of Scale/Scope Coefficient (Cost advantages in clinical trials, registration and price approvals; Learning Effects: R&D and knowledge spillovers of different drugs)
		H1 d.2: Probability of launch is higher for domestic launches.	Exists	+ Domestic Launch Coefficient (Evidence from the literature suggests domestic launches are quicker either due to the familiarity of the regulators with local firms or regulators favouring domestic firms)
	Product/ Molecule	H1 e.1: Therapeutically/commercially important molecules diffuse internationally faster (importance proxied by extent of global sales and global launch for the molecule)	Exists	+ Therapeutic Importance Coefficient (Therapeutic importance is a defining characteristic for quality since competition between on-patent molecules is based on quality. High-quality products should obtain faster approval as well as price mark-ups which increase incentives for faster entry)

3.4 EMPIRICAL RESULTS

Table 3.4 presents a number of competing specifications for the base case analysis to test for robustness. Complementary log log and Cox regression estimates (non-exponentiated) are reported for molecules that first launched globally after 1993. The results show that regulation has a significant impact on timing of launch through its effect on expected prices. In all regression specifications the estimates for price and volume are highly significant at the 0.001 level. The cloglog regressions with quadratic duration dependence include a second-order polynomial in time since global launch to control for the shape of the hazard with respect to time. Semi-parametric cloglog regressions assume constant hazard during each year following global launch and include dummies for each year following the first launch date worldwide.

Model (1) includes no control for country characteristics. Introducing controls for country characteristics (Model 2) slightly reduces the parameter estimates for expected price and expected market size as prices are positively correlated with some of the country characteristics such as GDP per capita. A positive parameter estimate for GDP per capita ($) indicates that the higher the GDP per capita, the higher is the probability of launch at a given time point *t* (the marginal effect of log GDP per capita, i.e. dy/d(Log GDP per capita) is 0.05, which essentially implies that if GDP per capita is multiplied by *e* =2.718, the hazard of launch increases by 0.05 (see Table C.6 in Appendix C.3.2 for marginal effects). Corruption perception index score relates to perceptions of the degree of corruption as seen by business people and country analysts (a score of 10 means highly clean whereas a score of 0 indicates a highly corrupt business environment)[80]. In contrast to findings of Kyle (2007), a market perceived less corrupt has quicker adoption of pharmaceutical innovation, which might be because of a larger sample in this study (or confounding factors).

Although previous studies find a positive impact of population on the timing of launch, estimates in Table 3.3 suggest that the log population is not a significant factor controlling for percentage of people above the age of 65, which means that measures of need appear to associate with higher diffusion. Underlying variables proxying the potential demand for medical care such as life expectancy and the age profile of the population (population above the age of 65 years) have a significant impact on timing of

[80] CPI scores are provided by the Transparency International. Available at: http://www.transparency.org/policy_research/surveys_indices/cpi/

launch (Model 2). While an older population profile speeds launch, a healthier population profile as proxied by life expectancy decreases the hazard of launch controlling for the population above 65 years old.

Note that country characteristics (except for GDP per capita) are no longer significant once country fixed effects are introduced (Model 3). Model 4 incorporates only country fixed effects to account for country heterogeneity. The parameter estimates for the expected price and volume are almost identical in Model 3 and Model 4. In addition, Akaike's information criteria (AIC) and Bayesian information criteria (BIC) are pretty close, which indicates that the two specifications are comparable in terms of statistical fit. Further robustness checks in the next section will, therefore, consider only country fixed effects.

The sign and significance of parameter estimates are consistent in the Cox and Cloglog estimates; however, Cox model estimates are consistently slightly higher than Cloglog regressions estimates, regardless of the specification of the duration dependence (i.e. whether it is quadratic in time since risk onset or semi-parametric). Adding more variables to control for country heterogeneity maintains the efficiency of the parameter estimates in both regressions; only a slight increase in the standard error of the expected price is observed. This could also be due to the fact that the number of observations is decreased for Models (2) and (3) as these models exclude South Africa. Cloglog and Cox regression estimates for parameters are highly comparable as expected. Although the Cox model is an approximation to the discrete case, lower values of AIC and BIC suggest that the discrete time implementation of the proportional hazard model provide a better fit. This is also suggested by more robust marginal effects in the cloglog regressions; marginal effects in the Cox model vary widely across model specifications (Table C.6). The fit and parameter estimates of the quadratic and semi-parametric specifications are comparable; the robustness checks in the next section, therefore, will report only results for the quadratic specification. Schonfeld residuals test rejected the proportionality assumption. Currently no test in Stata tests the proportionality assumption in a cloglog regression.

Table 3.4 Base Case Cloglog and Cox Estimates. Molecules with First Launch after 1993

Variable	*Cloglog quadratic duration dependence*				*Cloglog Semi-Parametric (year dummies)*				*Cox Semi-Parametric*			
	1	2	3	4	1	2	3	4	1	2	3	4
Log Lagged Avg Non-Generic Price/SU in Ctry-ATC4	0.085*** [0.01]	0.064*** [0.02]	0.074*** [0.02]	0.075*** [0.01]	0.086*** [0.01]	0.062*** [0.02]	0.071*** [0.02]	0.072*** [0.02]	0.098*** [0.01]	0.081*** [0.02]	0.093*** [0.02]	0.093*** [0.01]
Log Lagged Total SU in Ctry-ATC4	0.053*** [0.01]	0.049*** [0.01]	0.059*** [0.01]	0.059*** [0.01]	0.054*** [0.01]	0.048*** [0.01]	0.059*** [0.01]	0.058*** [0.01]	0.056*** [0.01]	0.057*** [0.01]	0.070*** [0.01]	0.069*** [0.01]
Years since global launch (t)	0.001 [0.02]	0.044 [0.03]	0.083** [0.03]	0.096*** [0.03]								
Years since global launch squared (t^2)	-0.007** [0.00]	-0.011*** [0.00]	-0.014*** [0.00]	-0.015*** [0.00]								
Log Population (000s)		-0.032 [0.02]	-3.207 [2.07]			-0.025 [0.02]	-3.024 [2.12]			-0.048 [0.02]	-2.545 [2.03]	
Population > 65 yrs		0.069*** [0.01]	0.001 [0.06]			0.071*** [0.01]	-0.004 [0.06]			0.066*** [0.01]	0.01 [0.06]	
Life expectancy in yrs		-0.245*** [0.02]	0.071 [0.12]			-0.253*** [0.02]	0.07 [0.12]			-0.229*** [0.02]	0.079 [0.12]	
Log GDP per capita ($)		1.263*** [0.18]	1.158* [0.58]			1.294*** [0.18]	1.273* [0.59]			1.120*** [0.17]	1.374* [0.58]	

Corruption Perception Index		0.081*** [0.02]	0.071 [0.06]			0.090*** [0.02]	0.082 [0.06]			0.089*** [0.02]	0.079 [0.06]	
Country Dummies	No	No	Yes	Yes	No	No	Yes	Yes	No	No	Yes	Yes
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calendar Year Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Number of Observations	58530	54794	54794	58530	58530	54794	54794	58530	58530	54794	54794	58530
LogLikelihood	-10727	-10058	-10001	-10541	-10697	-10023	-9962	-10497	-16860	-15848	-15790	-16682
Akaike's Info Criteria	21506	20179	20100	21171	21470	20129	20045	21108	33765	31751	31671	33449
Bayesian Info Criteria	21740	20455	20537	21575	21811	20503	20589	21620	33972	32001	32081	33826

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets). Non-exponentiated parameter estimates reported . Models (2) and (3) have fewer observations because data to control for country characteristics is not available for South Africa in the OECD database. Semi-parametric specification includes dummies for each year following global launch, in addition to dummies for calendar years.

Akaike and Bayesian information criteria indicate that the cloglog specifications overall fit the data better than the Cox semi-parametric model. The choice between semi-parametric and quadratic duration dependence is less obvious. While AIC is lower for the semi-parametric specification, BIC tends to be lower for the quadratic duration specification. Overall, their performance is very close. However, I use mainly the quadratic specification for robustness check (Section 3.4.1) due to the need to estimate fewer parameters.

The quadratic duration dependence specifications in the cloglog regressions provide an insight regarding how the hazard behaves over time following global launch (t), which cannot be deduced from Cox estimates directly. The evidence regarding duration dependence is mixed. Danzon and Epstein (2005) observe that the launch hazard increases with time since global launch for superior molecules. Danzon and Epstein (2008), however, find that hazards first decrease then increase with time since global launch. Estimates of duration dependence in this study differ from the already existing limited evidence in the literature. There is a strong indication that the hazard of launch first increases in time and then decreases. Ideally firms would like to launch in as many markets as possible to amortize the R&D outlays as quick as possible. However, since firms optimize strategic decisions jointly across markets, including launch and timing of launch decisions, delays may be incurred in markets where profits are jeopardized. The converging prices in Europe to avoid spillovers due to parallel trade and external referencing also indicate that firms strategically would like to launch early not to lose the competitive innovative edge of the new molecule as delays increase the chance of facing further competition later in time (Kyle and National Bureau of Economic 2007). The difference found between this study and Danzon and Epstein (2008) regarding duration dependence could be that the molecule set in this analysis includes molecules that are more recent (post 1993) and have a higher extent of global reach overall.

The estimates in Table 3.4 are consistent with the hypothesis that regulation reduces the speed of adoption of pharmaceutical innovation when price controls result in lower expected prices. This result is broadly consistent with prior findings in Danzon and Epstein (2005, 2008) , Kyle (2007) and Lanjouw (2005). Danzon and Epstein (2005, 2008) provide estimates both for superior and inferior therapeutic subclasses. Danzon and Epstein (2008) estimate a model which is closer to specifications provided in Table 3.4 by considering only expected price and market size at time t. Their estimates for expected price are 0.11 for superior brands and 0.07 for inferior brands. It is expected

that estimates in this study will fall broadly within the range of 0.07-0.11 since I assume no classification regarding the inferiority or superiority of the brand. My estimates for the cloglog specification with quadratic specification are in the range of 0.65-0.85, which is broadly consistent with findings of Danzon and Epstein (2008).

The marginal effect of the expected price in Danzon and Epstein (2008) is 0.0053 for superior molecules and -0.0001 for inferior classes. Marginal effect of expected price in this study is 0.003-0.004, which is again expected as superiority/inferiority of the therapeutic class is not modelled (and given that the molecule set is relatively more recent, the estimate is expected to be closer to the value for superior classes). The marginal effect of expected price is not significant for inferior brands in Danzon's estimates. Standard error estimates of expected price are slightly lower because I cluster by molecule-country rather than my molecule since autocorrelation may exist between consecutive error terms of a molecule-country pair [81].

I find new evidence regarding the impact of the expected market size. The literature so far has presented conflicting evidence regarding the impact of expected market size. Danzon and Epstein (2005, 2008) conclude that volume is not a significant determinant on the hazard of launch whereas Danzon, Wang and Wang (2005) find that it is a significant factor. In line with the findings of the earlier paper by Danzon, Wang and Wang (2005) my estimates for expected market size are highly significant and are within the range of 0.06-0.07. These estimates are pretty close to the estimate of 0.066 in Danzon and Epstein (2008) and 0.06-0.14 in Danzon, Wang and Wang (2005). In Danzon and Epstein (2008), the estimate of 0.066 is not significant for superior brands; however, the estimate of 0.12 for inferior brands is significant.

This finding suggests that it is not only price controls that may hamper timely launch. Price is only one factor that determines net present value. Any policy directed at restricting the market size may have a decelerating effect on timely innovation adoption; however, price as a regulation tool has a slightly larger impact. According to the marginal effect ∂Pr(launch at t)/∂(Log lagged expected market size) is 0.002. On the other hand, ∂Pr(launch at t)/∂(Log lagged expected price) is 0.003-0.004 (see Table C.6 in Appendix C for marginal effects).

[81] The marginal effect of price in the cloglog regressions is comparable to the marginal effect of the Corruption Perception Index score, life expectancy or the percentage of the population above the age of 65.

Price has gained strategic importance in the pharmaceutical industry during the past decade as price interdependency across international markets has increased due to external referencing and price knock-on effects in foreign markets through threat of arbitrage. This may drive firms to manipulate prices by drawing price levels closer across markets at the expense of foregoing some short-term profits in order to avoid negative impacts of price controls on firm's international launch strategies. I test for this by restricting the sample to the EU market where prices are interrelated due to external referencing and risk of parallel trade. I test for the significance of the extent of deviation between expected local price and the average EU price for the launching molecule (see Table 3.5). The absolute difference between the local expected price and the average EU price significantly decreases the hazard of launch. The sign of this difference or the interaction of the absolute difference with the sign of the difference are not statistically significant. This implies that pricing and launch strategies are now increasingly considering implications for future markets. Firms are global revenue optimizers and therefore strategic reactions to regulations may spillover to external markets. In particular, estimates in Table 3.5 suggest that global pricing strategies appear of increasing importance with firms launching their products at closer prices across markets as much as possible, and potentially reducing global prices assuming they cannot raise prices in the price-controlled markets.

The difference in estimates with respect to the innovativeness/superiority of the therapeutic class in Danzon and Epstein (2008) suggests that the parameter estimates for price and volume are sensitive to the choice of the molecule set. Danzon's findings indicate that for less important molecules volume is more important than price, which is expected because inferior molecules tend to be older and low-priced. Price spillovers for these products will not be an issue. Similarly, old products are unlikely to obtain a price premium through differentiation. Hence, firms launching older or less therapeutically important products will base their decision mostly on the expected market size. I tested for this by estimating the impact of price and volume for average molecules that launched in 10 markets, and for truly global molecules that launched in 20 markets and are potentially more important therapeutically/commercially. Estimates indicate that volume is more significant for average molecules and price is more important for more superior molecules (estimates for market size are 0.14 and 0.56; and estimates for expected price are 0.27 and 0.117 for global and average molecules respectively). An insight into the impact of therapeutic class age is provided in the robustness check

section on time effects where the age of the therapeutic group is interacted with the expected market size and the expected price of the launching molecule.

Regression estimates confirm the hypothesis that price regulation slows down the adoption speed of pharmaceutical innovation across the main OECD markets, controlling for the expected market size. The next section will investigate how robust the estimates are with respect to the inclusion of other covariates which have been theoretically and empirically suggested as key drivers of the firm decision of market entry; namely, the competitive environment, firm and molecule characteristics.

Table 3.5 EU Subsample: Test for Expected Price Deviations from the Average Price of the Launching Molecule

Variable	*Parameter Estimates by Cloglog (quadratic in t)*	
	1	2
Log Lagged Avg Non-Generic Price/SU in Ctry-ATC4	0.083*** [0.02]	0.079*** [0.02]
Log Lagged Total SU in Ctry-ATC4	0.056*** [0.01]	0.055*** [0.01]
Absolute Difference btw Local Expected Price and Average EU Price (ΔP = Local Expected Price – Average EU Price)	-0.124* [0.06]	-0.141** [0.04]
Absolute ΔP * Sign(ΔP)	-0.031 [0.07]	
Sign(ΔP) [a]		-0.001 [0.06]
Years since global launch (t)	0.106** [0.04]	0.105** [0.04]
Years since global launch squared (t^2)	-0.018*** [0.00]	-0.018*** [0.00]
Country Dummies	Yes	Yes
ATC1 Dummies	Yes	Yes
Calendar Year Dummies	Yes	Yes
Number of Observations	27322	27322
LogLikelihood	-5624.5	-5624.58
Akaike's Info Criteria	11326.99	11327.16
Bayesian Info Criteria	11647.4	11647.56

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors [in brackets] clustered at molecule-country level. Non-exponentiated parameter estimates reported.
[a] Sign Defined to be 1 if $\Delta P \geq 0$ and 0 otherwise.

Multicollinearity

Multicollinearity in independent variables increases estimates of parameter variance, produces parameter estimates of the incorrect sign and results in the unstability of the regression coefficient estimates. Multicollinearity issues for the base case models were investigated by computing the variance inflation factors (*VIF*). *VIF* is a measure of the multi-collinearity in a regression matrix (independent variables) and provide a measure of how much the variance of an estimated regression coefficient is increased because of collinearity. Collinearity can also be determined from pairwise collinearity between independent variables; however, correlation matrixes do not reveal higher order collinearity. *VIF*s are scaled versions of the multiple correlation coefficients between a given variable and the rest of the variables.The minimum value of a *VIF* is 1, which occurs when there is no correlation between the variable of interest and the rest of the variables. As a rule of thumb, *VIF* values greater than 10 indicate potential multi-collinearity problems. Collinearity should be removed by eliminating one or more variables and/or combining variables into one.

VIF estimates of the base-case models are presented in Appendix C.3.2.1. It can be observed that inclusion of both country dummies and variables such as GDP per capita, life expectancy, and population that control for destination country heterogeneity (Model 3) results in serious multicollinearity issues. Removing country dummies almost removes the multicollinearity issues (Model 2). Model 4 drops variables that define country heterogeneity (GDP per capita, life expectancy, population, corruption perception index) and keeps country dummies whereas Model 1 drops both dummies and the country heterogeneity variables. Both Models 1 and 4 are free from multicollinearity problems as all VIFs are less than 10. In the robustness checks, I drop country-specific variables and keep country dummies to account for country effects. Robustness checks assume quadratic duration dependence as semi-parametric and parametric specifications have similar fit but the parametric specification is more parsimonious in the number of parameter estimates.

3.4.1 Robustness Checks

Robustness checks were carried out by estimating the Cox model and the Cloglog model with the quadratic specification (since estimates for quadratic duration dependence are very similar to the semi-parametric specification). However, only

estimates for the Cloglog model are presented since the marginal effects of the Cox model in the base case did not turn out to be very stable.

3.4.1.1 Time Effects

Time may affect regression estimates in several ways. First, macroeconomic trends in the sector may have an impact on price levels. This is accounted for by including dummies for each calendar year in all regressions. Second, time captures information about the relative innovativeness of new molecules. When a new molecule is about to launch, it represents incremental (or breakthrough) innovation compared to the molecules in its therapeutic subclass. The longer the time lapse from global launch, the higher is the probability that new competitors will enter to compete against the molecule lowering its comparative therapeutic advantage. To capture the impact of time elapsed since first global launch on price and volume, the two main variables of interest, both expected price and volume are interacted with time since global launch.

Estimates so far have been obtained for molecules that launched after 1993, which is the year when a single European Market was established. The observation period, however, is from 1999 to 2008 since price and volume information in the database is available only during this period. This implies that molecules with first global launch in [1993, 1999) are left-truncated. In semi-parametric models left-truncation is easily dealt with by omitting the subject from all binary outcome analyses during the truncation period since the subject could not have failed in that period (Cleves, Gould et al. 2008). The dummy "First Launch Before 1999" accounts for left-truncated molecules and tests if the hazard of launch statistically is different for these molecules.

Table C.11 (Appendix C.3.2.2) presents the robustness checks with respect to time effects. The marginal effects of expected price and market size remain unchanged. Time interactions of price and volume are significantly negative, which suggests that the impact of price and volume decays over time following the global launch of the molecule. Model 2 and 3 estimates indicate that left-truncated molecules (molecules that launched first before 1999) have a significantly lower hazard rate compared to molecules that entered launched after 1999. This dummy also partially captures innovation as left-truncated molecules are older, which suggests that innovative molecules diffuse faster. Model 4 tests for the effect of excluding left-truncated molecules by estimating parameters only for molecules that launched after 1999. The estimates for price and volume are slightly lower and the standard errors are higher due

to the loss in the number of observations. Marginal effects, however, are comparable to the results in previous models.

Finally, as mentioned before parameter estimates of t and t^2 show the duration dependence of the hazard with respect to time since global launch. Assuming the form $a.t + b.t^2$, the hazard achieves its maximum at $t = -b/2a$. For all 4 model estimates $-b/2a$ range from 4.5-5.5 years. This implies that the probability of launch in an average market is highest around year 5 after global launch, and thereafter, the probability of launch starts to decline. This value could be lower or higher depending on the individual destination country (e.g. US and UK will have the hazard maximized at a lower t).

I also consider the interaction of therapeutic class age with expected price and market size to assess how the age of the therapeutic class affects the importance of price and volume (see Table C.12 in Appendix C.3.2.2). Age of the therapeutic class ATC4 is defined by the difference between time t and the first available launch date in the ATC4 among the 20 markets in the dataset. Expected price and market size are still significant after accounting for the age of the therapeutic class. Table C.12 shows that the importance of expected price and market volume is reduced as the therapeutic class gets older; this is because newer classes represent more innovative products. Interaction of time since global launch of the molecule and expected price ceases to be significant once expected price is interacted with therapeutic class age (these two interactions are highly correlated 0.68).

3.4.1.2 Market Structure and Competition

Regression estimates presented in Table C.13 (Appendix C.3.2.2) confirm that intermolecular competition is more influential on the decision of entry compared to the extent of generic competition. The number of competitor molecules in the same ATC4 significantly increases the hazard of launch, while the number of molecules with generic competition has no effect on the launch decision of new molecules. The observation that extent of competition increases entry is consistent with findings of Kyle (2007). Regulation, therefore, may have another indirect effect on entry through reduced competition since lower prices result in reduced entry. In fact, estimates for the effect of existing competition are much higher than the price effect. The marginal effect of expected price is 0.003-0.004 whereas marginal effect of log number of competitors is 0.12.

Due to differences in definition of branded-branded or branded-generic competition, parameter estimates for competition in this study are not directly comparable to prior studies in the literature. Kyle considers the count of drugs in a given therapeutic class-country; however, her definition of entry includes different class combinations for a given molecule, i.e. different indications. Danzon and Epstein (2005, 2008), on the other hand, consider only the number of generic manufacturers per molecule and include a dummy variable to model the first entry into a therapeutic subclass and do not have a measure of the extent of branded-branded competition other than the average competitor prices.

Model 1 (Table C.13) shows that subgroup concentration, as expected constitutes a barrier to entry. The more concentrated the subgroup is, the lower is the probability of entry at a given time *t*. Models 3 and 4 show that expected market size and subgroup concentration are no longer significant once the number of competitor molecules is included as a control variable. This effect occurs because number of competitor molecules and sales volume in ATC4 are positively correlated (correlation is 0.22 and is significant at the level of 0.001). Similarly, concentration is negatively correlated with the number of molecules (though the correlation is relatively weaker at the level of 0.08). Marginal effects of price and time interactions are robust to the inclusion of competition variables.

3.4.1.3 Firm Characteristics

Firm heterogeneity as expected plays a significant role in international launch strategies for pharmaceutical innovation (Kyle 2006). Table C.14 (Appendix C) suggests that firm effects are at least as significant as price and market size effects. In particular, variables that control for firm economies of scale have the same marginal effect on the hazard of launch. Economies of scope as proxied by firm's global pharmaceutical sales and number of countries the firm has launched before have even slightly higher impact than regulation.

In line with findings of Kyle (2007) the number of countries the firm has launched in is significant and has a marginal effect of 0.009; i.e., ∂Pr(launch at *t*)/ ∂(Log number of countries launched in) is 0.009. Kyle's estimate of marginal effect for international launch experience is 0.0003; however, in her case this figure corresponds to ∂Pr(launch

at $t)/\partial$(number of countries launched in). These two marginal effects are related as follows:

$$\frac{\partial y}{\partial x} = \frac{\partial y}{\partial \ln x} \cdot \frac{\partial \ln x}{\partial x} = \frac{\partial y}{\partial \ln x} \cdot \frac{1}{x}$$

The average number of countries a firm has launched is 16. Plugging in $x = 16$ and $\partial y/\partial \ln x = 0.009$ gives $\partial y/\partial x = 0.0005$, which is close to Kyle's estimate.

Similarly, marginal effect of local experience is 0.003. This variable is not directly comparable to the estimate of 0.0013 in Kyle (2007) since number of drugs in Kyle's case includes additional indications for a given molecule. The log of firm sales has a positive significant parameter estimate around 0.12 and a marginal effect of about 0.004. Danzon, Wang and Wang (2005)'s Cox estimate of log firm sales is 0.208 (also significant at the level of 0.001) (Cox regressions in general result in slightly higher parameter estimate)[82].

Results in Table C.14 indicate that the diversity of firm's prior portfolio is associated with quicker launch, which differs from prior evidence that a higher number of drugs in the firm portfolio reduces the extent and speed of launch (Kyle 2007). In terms of magnitude, past portfolio diversity, has as big effect as the average expected price.

Finally, I find no robust evidence that domestic launches are associated with quicker international diffusion. The effect of domestic launch is significant in Model 4 but not in Model 3. Home advantage has mostly been associated with speedy launch in the literature. However, Danzon and Epstein (2008) suggest that domestic launch may be associated with industrial policies of supporting the local pharmaceutical industry and restricted to countries such as France, Italy, Spain, Switzerland and Japan where the local pharmaceutical industry plays a role. I tested for this observation, by creating an interaction with these 5 markets and firms headquartered locally. However, I obtained no evidence that local firms in these markets launch quicker compared to firms that are not headquartered in these countries.

[82] See the Appendix for a Box plot of the distribution of Cox and Cloglog parameter estimates from the robustness checks

3.4.1.4 Molecule Characteristics

Estimates presented in Table C.15 (Appendix C.3.2.2) suggest that heterogeneity in molecules also plays a key role in explaining launch hazards. In particular, the extent of global reach has the biggest impact on launch hazard. Marginal effect of log of total markets reached is 0.059. Given that the average number of countries a molecule launches is $x = 18.3$, marginal effect of the extent of global reach on launch hazard is $\partial y/\partial x = 0.003$ for an average molecule, which is close to Kyle (2007)'s estimate of 0.004. Log of molecule sales has a significant positive marginal effect of 0.003, and is comparable to the impact of regulation. Overall, this suggests that regulation will have a more pronounced effect on non-global molecules, or therapeutically less important molecules.

3.4.1.5 Regulation: EU subsample

Finally, the country set was restricted to European countries in order to check for the impact of external referencing and launch in a high-priced EU market. There is an indication that external referencing slows down adoption of innovation and that launch in a high-priced EU market compared to launch in a lower priced EU-market increases the hazard by 0.042 for molecules that launched first after 1993 (Table C.16, Appendix C.3.2.2). The marginal effect of launch in a high-priced EU country is 0.051 for molecules that first launched after 1999, implying that the importance of price has risen after 1999. Accordingly, the parameter estimate for expected price is higher when more recent launches are considered.

Comparison of Cloglog and Cox specifications using Akaiake and Basyesian information criteria indicates that discrete-time specification with Cloglog is preferable over the continuous-time Cox specification. Figure C.1 and Table C.17 – C.18 present a comparison of the parameter estimates for expected price and volume by Cox and Cloglog estimation[83]. Summary statistics for the mean show that Cox estimates overestimate the parameters compared to the cloglog specification.

A summary of the main hypotheses tested, expected and estimated coefficient signs are presented in Table 3.6.

[83] For brevity Cox estimates are not presented in the robustness check section

Table 3.6 Comparison of Expected and Estimated Signs of the Coefficients

Factor	*Hypotheses*	*Evidence from the Literature*	*Expected Sign of the Coefficient*	*Estimated Sign of the Coefficient*
Regulation	H1 a.1: High expected prices increase the speed of cross-country diffusion of pharmaceutical innovation; therefore, price regulations that reduce prices result in delayed access to pharmaceutical innovation.	Exists, but limited	+ Price Coefficient (Expected due to price spillover effects, also high-priced markets usually have fewer pricing controls which allows quicker market access)	+
Market	H1 b.1: Pharmaceutical innovations with a higher expected market size (sales volume in ATC4) diffuse internationally faster, controlling for the effect of expected price.	Contradictory	+ Market Size Coefficient (Controlling for expected prices, high-volume markets [in $] should have quicker launch to maximize returns on R&D and benefit from longer market exclusivity)	+
	H1 b.2: Corruption reduces the speed of pharmaceutical innovation adoption	Contradictory (- in tele-communications, + in pharma-ceutical sectors)	- Corruption Coefficient (Corruption results in complicated entry mode, favours joint ventures and partnerships, increases entry costs [due to time costs as well as demand for bribes] and diminish potential firm-level growth)	-
Competition	H1 c.1: A higher therapeutic subgroup concentration (molecule concentration in ATC4) reduces the hazard of launch.	No evidence	- Concentration Coefficient (According to the industrial organization literature concentration reduces the equilibrium level of entry in several industries)	-

	H1 c.2: Branded-branded competition is a significant determinant of the launch hazard and more important compared to the extent of generic competition in the therapeutic group.	Exists, but limited	- Branded Competition Coefficient (For new molecules the most imminent competition is branded competition. Competition drives prices down if differentiation is not strong enough and reduces incentives for entry)	No Significant Evidence
Firm	H1 d.1: Firm economies of scale and scope increase the hazard of launch (proxied by global firm sales and number of molecules in portfolio)	Exists	+ Economies of Scale/Scope Coeff (Cost advantages in clinical trials, registration and price approvals; Learning Effects: R&D and knowledge spillovers of different drugs)	+
	H1 d.2: Probability of launch is higher for domestic launches.	Exists	+ Domestic Launch Coefficient (Evidence from the literature suggests domestic launches are quicker either due to the familiarity of the regulators with local firms or regulators favouring domestic firms)	No Significant Evidence
Product/ Molecule	H1 e.1: Therapeutically/commercially important molecules diffuse internationally faster (importance proxied by extent of global sales and global launch for the molecule)	Exists	+ Therapeutic Importance Coefficient (Therapeutic importance is a defining characteristic for quality since competition between on-patent molecules is based on quality. High-quality products should obtain faster approval as well as price mark-ups which increase incentives for faster entry)	+

3.5 CONCLUSIONS

This chapter aimed to investigate how regulation, in particular price regulation, affects the adoption of innovative pharmaceutical products across the main OECD markets during 1999-2008. I have investigated the impact of regulation on adoption of a recent set of molecules that have diffused across more than 10 markets within the OECD, controlling for the external and internal firm environment. Results suggest that the effect of price regulations on timing of launch is significant and robust across different specifications. High ex-ante price expectations increase the speed of cross-country diffusion of pharmaceutical innovation. Regulations that reduce prices or put limits on the sales volume result in delayed access to pharmaceutical innovation.

Results suggest a statistically significant and robust effect of price on timing of launch across different specifications. High ex-ante price expectations increase the speed of pharmaceutical adoption internationally, which is consistent with hypothesis H1 a.1 (Higher expected prices increase the speed of cross-country diffusion of pharmaceutical innovation. Regulations that reduce prices or create price linkages across markets may lead to delayed access to pharmaceutical innovation as a result of reduced incentives to entry, profit implications in subsequent markets and strategic firm delays; empirical results would indirectly support this argument. Consistent with hypotheses H1 b (Pharmaceutical innovations with a higher expected market size diffuse internationally faster, controlling for the effect of expected price), findings indicate a significant and robustly positive market size effect that increases the likelihood of new pharmaceutical adoption.

Regulation is a key factor in the external firm environment, as it defines not only the attractiveness of the local market but also creates interdependencies across different countries. The internal firm environment, however, also has a substantial effect on the speed of adoption of pharmaceutical innovation. In particular, firm economies of scale and molecule's therapeutic importance grant substantial advantages for timely rollout internationally. Significant firm and molecule heterogeneity exists, which is consistent with hypotheses H1 d.1 (Firm economies of scale and scope increase the hazard of launch) and H1 e.1 (Therapeutically or commercially important molecules diffuse internationally faster). Products of larger firms that have launched in more countries and have more local experience are less prone to delays in adoption, controlling for expected prices, market structure and market size. Firms with more diverse R&D portfolios (as

proxied by the number of molecules that have accessed the market successfully) have a higher probability of quick launch, which demonstrates advantages of economies of scale. Contrary to what the prior literature suggests, I find no significant advantage to domestic launch, which contradicts hypothesis H1 d.2 that probability of launch is higher for domestic launches.

Regulation has a non-homogenous effect on molecules with different therapeutic value. More recent molecules, and hence more innovative molecules, have higher probabilities of launch. This is partially attributable to the price effect of regulation, the speed of market authorization and price approval negotiations. Regulatory authorities generally grant a price mark-up to products that offer therapeutic novelty or public health advantages with significant implications on health budgets. Tentative evidence suggests that for molecules that are more recent price has a greater impact whereas for old molecules volume is strategically more important than price.

Consistent with hypothesis H1 c.1 higher therapeutic subgroup concentration constitutes a market barrier to timely adoption of new technologies, which confirms the importance of policies directed at fostering competition in the pharmaceutical sector. Regulation, therefore, affects market entry decisions both directly and indirectly through its effect in prices and market structure/competition respectively. Consistent with hypothesis H1 c.2, branded-branded competition is far more important in determining firm's launch strategies for new molecules compared to existing generic competition. This is mainly explained by the fact that already existing generic competitors are not exact substitutes for new molecules and thus do not compete directly.

Findings in this chapter suggest several policy implications. First, price regulations slow down the adoption of pharmaceutical adoption on a global scale and may impose welfare losses, particularly when the delayed innovations are cost-effective from a societal perspective. Although lower prices increase static efficiency in the short term by reducing the mark-up of price over marginal cost, empirical evidence from this chapter suggests that price controls could have negative implications on dynamic efficiency by reducing incentives to (timely) entry and the extent of competition. Delays in adoption reduce the net present value of R&D investments by delaying cash flows and shortening the exclusivity period, which has been observed to reduce future R&D outlays and innovation (Giaccotto, Santerre et al. 2005). That said, the optimal form of

pharmaceutical regulation and the degree of price mark-up consitent with dynamic efficiency are not addressed here and lie outside the scope of this thesis.

From a public health perspective, late adoption and lack of access to new drugs may lead to compromises in health outcomes (Schoffski 2002), shift volume to older molecules of lower therapeutic value (Danzon and Ketcham 2004) and compromise the quality of health care (Kessler 2004; Wertheimer and Santella 2004). Innovative medications offer economic benefits by avoiding expenditures on other forms of medical care (such as hospitalization) as well as reducing missed work days (Lichtenberg 1996; Lichtenberg 2003a; Hassett 2004; Lichtenberg 2005). Again, in a wider context, the assessment of short-term efficiency gains brought about through price regulation should be weighed against potential long-term implications on public health outcomes and dynamic efficiency. This study has merely provided evidence on the impact of price on adoption, and the continuation of debate over static and dynamic efficiency gains falls outside the scope of this work.

Second, findings suggest that industrial policies should promote competition in the pharmaceutical sector. Extensive price controls could reduce incentives to entry and result in a less competitive environment to stimulate further innovation. Third, local controls can affect firms' launch decisions in foreign markets and impose welfare losses, especially in lower-priced markets. Finally, due to scale advantages in international roll-out strategies, price controls may increase incentives for mergers and acquisitions, further increasing concentration levels and barriers to entry.

This chapter contributes to the existing literature in several ways. First, the dataset allows exploitation of the variation both over time and across molecule-country pairs. The robustness of the results has been assessed by different duration specifications and alternative proxies for risk factors. Second, the dataset is more comprehensive and up-to-date than comparable empirical studies in the literature. Third, the analysis makes use of reliable price and volume information. The price effect is calculated controlling for firm and molecule heterogeneity that could bias the estimates if omitted. Finally, the analysis is carried out for potentially global molecules, which ensures findings are relevant from an international perspective.

The analysis, however, presents several limitations. Expected prices and market competition are assumed to be determined exogenously, although the potential impact of endogenous affects has been partially accounted for by incorporating lagged prices

and undertaking subsample analysis. A future extension could involve endogenizing prices and entry. Second, the constituents of launch delays cannot be completely isolated since data regarding regulatory authorization and price review times are not available. Finally, overall societal welfare implications cannot be inferred from this analysis. Both markets and government are imperfect institutions; it remains an open question which institution accomplishes overall pharmaceutical policy objectives in a more efficient and equitable manner.

CHAPTER 4

4 Price Regulation and the Adoption of Generic Competition: Evidence from the major OECD markets during 1999-2008

4.1 INTRODUCTION

Expanding pharmaceutical expenditures and growing pressure on budgets due to the recent financial crisis has further increased the emphasis on value for money in public policy making. Generics that are by definition cost-effective alternatives to branded medicines offer the most visible source of savings and efficiency gains. Delays in the entry of generic competition following patent expiry imply substantial opportunity costs for the sustainability of healthcare systems. Despite the increasing economic importance of generic competition, there is surprisingly little empirical evidence on generic adoption and drivers of delays across major pharmaceutical markets. The purpose of this chapter is to empirically examine how different pricing regulations influence the adoption of generic competition using price and volume data from 1999 to 2008 in the OECD market.

A generic drug is chemically bioequivalent to the originator reference product with the same qualitative and quantitative composition in active ingredients, same form, route of administration, safety, and efficacy (Scott Morton 1999; Lichtenberg and Philipson 2002). Given little potential for differentiation, generics predominantly engage in price competition resulting in a significant pressure on branded price levels and market competition. Branded share of market revenues in the US within 2 yrs of patent expiration generally falls by 50% (Griliches and Cockburn 1994). Similarly, average prices in Europe drop by 25% after the second year exclusivity is lost (DG Competition 2009). Generic competition, therefore, improves equity of access to pharmaceutical treatment by lowering procurement prices.

Timely generic entry is important not only from a static efficiency perspective but also from a dynamic perspective. Incentives to invest in future innovation are higher when branded manufactures face generic competition. Economic theory predicts that monopolists have little incentive to develop new products that will compete directly against their products (known as the replacement effect) (Tirole 1990). Resources saved by payers because of generic use can be transferred to stimulate future innovation in the branded sector, ensuring both the improvement in health benefits with new medicines

and the sustainability of the generic sector. Given aging demographic profiles, growing trend towards chronic life-style diseases, and expected patent expiries, policy measures conducive to fast generic adoption and diffusion offer significant savings in the near future (Gorka 2009).

From a strategic perspective, timing to market is a key dimension of competition in the generic sector. Legislations in certain markets grant market exclusivity to the first generic company that files for authorization (e.g. in the US exclusivity is 180 days). In general, first generics are expected to launch at higher prices and maintain generic market leadership as the demand-side may be reluctant to switch across alternative generics. Pharmacies, for instance, would avoid stocking multiple generics for a given molecule due to efficiency concerns (Competition Bureau Canada 2007).

Regulatory and financial barriers to market entry in the generic sector are highly asymmetric compared to the branded sector. Sunk costs are much lower in the generic sector since substantial R&D outlays for drug discovery and clinical trials to prove safety and efficacy are not required[84]. The cost of a bioavailability test has been estimated to be 18 times cheaper than the average costs of safety and clinical evaluation, which allows generics prices to be 20-80% cheaper than originators (Pharmaceutical Manufacturers Association 1993; Simoens 2007). Canadian Generic Drug Sector Study (2007) estimates bioequivalence study costs in the range of $1-1.5m per product. Second, the technical and market risks faced by generic manufacturers are much lower as the therapeutic and commercial success of the originator has been tested by the time of patent expiry. Third, countries in the OECD have adopted several measures to further ease generic entry: generic substitution, Bolar provisions, market exclusivity grants to first generics (US), and generic reference pricing (the relevant legislations are discussed in Chapter 2 and a summary table is provided in Appendix D, Table D.1). Additional discussion about generic substitution in the US-EU5 is presented in Appendix A.3.

Bolar provisions allow generic manufacturers to experiment with a drug before the expiry of the patent and apply for market authorization (MA). Bolar provisions were granted in the US by the Hatch Waxman Act in 1984, and Europe followed with a delay of twenty years in 2004. In countries such as the US, UK and Germany, generic medicines obtain immediate price and reimbursement approval following MA. In

[84] Entry costs are greatest for the first generic due to legal challenges and costs fall for follower generics.

contrast, most markets that require price and reimbursement approval may delay market access of generic products. Time delays for generics following MA were on average 153 days in the EU, with a significant variation across Member States depending on local pricing and reimbursement (P&R) regulations (Bongers and Carradinha 2009). Generic price may be established as a percentage of the reference product, as the average price in reference countries, as a maximum (index) price or negotiation-based price (price-volume trade-off).

Overall, the time it takes a generic drug from the research lab to the patient is 3-5 years, whereas branded drugs take about 12 years. On the other hand, generics may be subject to behavioural barriers to adoption and diffusion as a result of virtual perceived quality differences between branded and generic products. In particular, price-insensitive consumers or physicians may show a strong loyalty for brand-name drugs (Frank and Salkaver 1992), and physicians may have sticky prescribing habits that hamper switching to generic drugs (Hellerstein 1998; Coscelli 2000).

The main hypothesis in this chapter is that the variation in the timing of first generic availability for a given molecule can be explained by ex-ante price and volume expectations. Free-priced markets not only avoid additional delays due to P&R approval but also offer higher incentives to market entry as a result of higher generic prices and higher generic penetration. Generic volume varies significantly across countries due to different demand-side policies, consumer attitudes and healthcare infrastructures. I hypothesize that ex-ante volume expectations is a significant determinant of probability of launch given lower profit margins and faster price erosion in the generic sector once fierce competition sets in.

Although issues related to the utilization of generic drugs and their impact on the on-patent sector have been studied more extensively, there is currently no study in the literature that empirically analyzes differentials in launch for first generics across a comprehensive set of markets. This chapter aims to provide preliminary evidence to fill this gap in the literature. Our empirical strategy uses discrete-time duration analysis to estimate the impact of regulation on the probability of launch across twenty pharmaceutical markets controlling for market size, expected competition, molecule and firm heterogeneity.

The remaining of the chapter is structured as follows: Section 4.2 discusses the literature and sets the theoretical framework; Section 4.3 describes the methodology

used; Section 4.4 presents the estimation results and finally Section 4.5 discusses the findings and policy implications.

4.2 GENERIC ENTRY: EVIDENCE FROM THE LITERATURE

4.2.1 Regulation as a Barrier to Generic Entry

Market power of patent-protected medicines reduces allocative efficiency. However, it is needed to stimulated innovation since the prospect of appropriating the R&D investments is the main push force for firms to improve drug quality and address unmet medical need. Eliminating market power would be detrimental to firms' incentives to innovate and would severely undermine dynamic efficiency and technological progress that drives health improvements and economic growth. On the other hand, it is also desirable to spread the benefit of innovation to other firms to stimulate future competition. This trade-off between static and dynamic efficiency is at the core of pharmaceutical policies and has generated a vast literature on the optimal length of patent life. A too short patent protection period would not grant enough appropriability to innovators but a too long period would preclude rival firms from challenging the incumbent innovator. In the pharmaceutical context, savings due to generic entry could be used to reimburse new innovative, cost-effective medicines. Therefore, policy makers would like generic competitors to enter the market as soon as patent protection expires. Regulations such as Bolar exemptions have enabled generic manufacturers to carry out necessary bioequivalence tests on on-patent medicines without infringing patents in the US since 1984 and in the EU since 2004.

Within Europe, pricing of generic medicines has remained an area of national responsibility. The impact of different generic pricing policies on adoption and patient access has remained largerly unexplored. The following sections summarize the available evidence on the impact of regulation on the extent and timing of generic entry.

4.2.1.1 Impact of Regulation on the Extent and Timing of Generic Entry

Evidence from North America

Most of the evidence regarding generic entry belongs to the North American market, partially because the generic sector has matured faster in the US as a response to provisions of the Hatch-Waxman Act. Analogous regulations have been enacted in Europe but with a lag of about 20 years. Previous empirical studies on generic entry

have demonstrated that pre-entry market size and expected profits (Grabowski and Vernon 1992; Scott Morton 1999; Scott Morton 2000; Reiffen and Ward 2005; Saha, Grabowski et al. 2006; Appelt 2009; Iizuka 2009; Moreno-Torres, Puig-Junoy et al. 2009), firm and drug characteristics (Bae 1997; Scott Morton 1999), the brand-name drug's goodwill stock (Hudson 2000; Hurwitz and Caves October 1988) as well as pharmaceutical price regulation (Danzon and Chao 2000b; Ekelund 2001; Moreno-Torres, Puig-Junoy et al. 2009) and market structure/competition (Bae 1997; Iizuka 2009; Moreno-Torres, Puig-Junoy et al. 2009) are important factors in the generic firms' entry decision. Moreover, entry dynamics differ strongly across therapeutic-classes (Saha, Grabowski et al. 2006).

There is a significant body of literature that investigates the extent of generic entry; however, the evidence on the differentials in adoption is scarce. Bae (1997) investigates the speed of generic entry post-patent expiry in the US market using a proportional hazard model with continuous failure times (Bae 1997). Higher revenues before patent expiry, proxied by the sales revenue of the brand-name manufacturers before patent loss, are associated with higher generic entry. Bae (1997) finds that the higher the degree of competition as proxied by the number of brand-name competitors, the slower the generic entry. Saha (2006) shows that the number of new generic entrants is lower as the number of generic incumbents increases due to lower profit expectations (Saha, Grabowski et al. 2006). Frank and Salkaver (199&) find direct evidence that revenue and the extent of entry are positively related for off-patent molecules during 1984-1987 (Frank and Salkever 1997). Similarly, Hudson (2000) identifies market size (original brand sales, deflated by the consumer price index) at patent expiration as the most significant determinant of generic entry in the US, the UK, Germany, and Japan. Increases in sales reduces the generic entry lag after patent expiration in these markets (Hudson 2000).

According to evidence from the US market during 1984-1994, generic firms enter markets with similar operating conditions to the drugs they already produce (Scott Morton 1999). Generic entry rates are also affected by the proportion of hospital sales. Drugs with higher hospital sales and drugs that treat chronic conditions exhibit higher entry rates in the US during 1986-1991. The number of brand-name competitors reduce generic entry whereas no significant evidence is found regarding the number of off-patent brands in the same therapeutic-group (Scott Morton 2000). In contrast to findings from the US studies by Bae (1997) and Scott Morton (2000), a more recent study by

Magazzini et al observes that different brand names have a positive effect on generic entry in USA, UK, Germany, and France (Magazzini, Pammolli et al. 2004).

Evidence from Europe

Several studies have identified pharmaceutical price regulation (Danzon and Chao 2000b; Ekelund and Persson 2003; Moreno-Torres, Puig-Junoy et al. 2009) as a significant factor in generic firms' entry decision. However, the evidence on the impact of different regulations on generic entry is limited.

Rudholm (2001) analyzes generic entry during 1972-1996 in the Swedish market. Similar to the findings from the American market, Rudholm (2001) finds that expected profits are associated with higher generic entry in a regulated environment. The shorter the patent protection for the branded product, the higher the number of generic entrants (Rudholm 2001). Subsequent evidence from the Spanish market confirms that drivers of generic entry in a market with tough price regulations are similar to those in less regulated markets. Moreno-Torres et al (2009) estimate the number of generic firms that enter into different active ingredient markets during 1999-2005, ignoring firm's follow-on launches with different forms and doses. Both a higher number of generic incumbent firms and a higher number of molecules per therapeutic group decrease the average number of generic entries. This study concludes that reference pricing squeezes the potential market for generics by lowering branded drug prices and depriving generic firms of their main competitive advantage (Moreno-Torres, Puig-Junoy et al. 2009). Generic use is discouraged if originator prices cluster around the reference price level as potential profits for generics are reduced (Simoens and de Coster 2006). Findings from a Swedish study confirm that the reference price system on average decreases the probability that generics are launched (Ekelund and Persson 2003).

Evidence from Japan

More recently, Iizuka (2009) examines generic entry in the Japanese pharmaceutical market during 2003 - 2005. The sample used in the analysis is comprised of all prescription (ethical) drugs that experienced generic entry in 2004, 2005 and 2006. Iizuka examines the entry of generics only during the first year once generic entry becomes possible by using pooled cross-section data and estimating a count model

(negative binomial model). 57 molecules are included in the analysis, which corresponds to 97 different markets (molecule-form-strength triple [85]).

Contrary to findings from the US market, evidence from Japan indicates that fewer generics enter if the drug is more frequently prescribed in large hospitals and at institutions where prescribing and dispensing are separated. This is due to price regulation in Japan that provides higher price-cost mark-ups for institutions that both prescribe and dispense generics. Also, there are significant behavioural barriers as doctors keep strong connections with medical schools where professors have high-level involvement in developing brand-name drugs and treatment guidelines. A more competitive branded sector in Japan, proxied by the number of brand name drugs already in the market, negatively affects generic entry. Economies of scope in entering multiple markets and brand revenues are important determinants that explain generic entry in the Japanese market (Iizuka 2009). The contribution of this study is that it uses micro-data rather than aggregate, market data, and can therefore control for demand heterogeneity.

4.2.1.2 Impact of Regulation on Generic Penetration

Studies that address generic penetration and impact of generics on branded product prices have highlighted the significant role of price regulation. The literature suggests generic diffusion may suffer in markets that have strict regulations for on-patent product prices. Although price control measures may be effective in cutting prices and hence curbing pharmaceutical expenditures, in the long run more stringent price regulation (as in Austria, Belgium, France, Italy, Portugal, Spain) may result in limited diffusion of generics and reduced incentives for generic entry (Danzon and Chao 2000a; Garattini and Ghislandi 2006).

Weaker price regulation is not only associated with higher levels of entry but also more intense competition among generic manufacturers as well as higher competitive pressure on branded prices. Free priced markets (US, Germany, the Netherlands and the UK) generally have higher drug prices and a higher originator-generic price differential, increasing incentives for generic entry. In price-regulated markets with reference pricing systems, generic use might be further discouraged if originator prices cluster around the reference price level, which lowers potential profits for generics and

[85] Molecule: active ingredient of the drug. Form: oral, topical vs injectable. Strength: the amount of active ingredient

discourages generic entry and diffusion. Generic penetration can be promoted by integrating demand-side policies (physician budgets with rewards for surpluses and sanctions for deficits, generic substitution schemes that financially reward the pharmacist, patient co-payment schemes) with supply-side policies (Simoens and de Coster 2006).

4.2.2 Strategic Barriers to Generic Entry

Economic theory predicts that generic entry should lead to a sharp decline in the price and market power of the originator molecule. To counteract market erosion induced by generic entry, innovator companies have developed several strategies for product life-cycle management to counteract the combined impact of increasing patent losses over time and the decrease in pharmaceutical R&D efficiency (Karwal 2006). A significant body of literature analyzes the dynamics of branded-generic competition after patent expiry and strategies originators pursue to minimize the impact of generic entry on life-cycle profits (Caves, Whinston et al. 1991; Grabowski and Vernon 1992; Frank and Salkever 1997; Suh, Schondelmeyer et al. 1998; Aronsson, Bergman et al. 2001; Magazzini, Pammolli et al. 2004; Lexchin 2006).

4.2.2.1 Generic Entry-Deterring Strategies by Originator Firms

Based on the bioequivalence requirement generics constitute a perfect substitute to the branded product. Economic theory predicts that generic entry should lead to a sharp decline in the price and market power of the originator molecule. Innovators have increasingly become more aggressive in defending their brands market share at the face of generic competition and have developed new strategies for product life-cycle management to counteract the combined impact of increasing patent losses over time and the decrease in R&D efficiency (Karwal 2006).

A significant body of literature analyzes the dynamics of branded-generic competition after patent expiry and the strategies of originators to minimize the impact of generic entry on life cycle profits (Caves, Whinston et al. 1991; Grabowski and Vernon 1992; Frank and Salkever 1997; Suh, Schondelmeyer et al. 1998; Aronsson, Bergman et al. 2001; Lexchin 2004; Magazzini, Pammolli et al. 2004). Traditionally, innovators have defended market shares through patent protection strategies that include patent clusters and patent litigations to restrict generic penetration. The patent holder may opt for obtaining additional patents for the improved version of the base product while making

the old one obsolete. Also, line extensions can be created by obtaining patents for use in the treatment of additional diseases (Pearce 2006)[86].

Other common strategies are reformulation of the original molecule to shift demand; switching from prescription to over-the-counter (OTC) status that allows direct to consumer marketing in the US and defensive pricing. Reformulation may involve combining the active ingredient with another molecule; changing the dosage, route of administration or creating controlled release versions. Defensive pricing involves lowering the price of the originator molecule for certain formulations or doses or discounts for repeat prescriptions. Another pricing strategy to maintain market share is based on market-segmentation by consumer brand loyalty. In free-priced markets, the originator may increase off-patent molecule prices to capture more revenue from the insensitive segment of the market and retain shares, which is known as the "generic paradox" (Frank and Salkaver 1992; Frank and Salkever 1997; Regan 2007; Schweitzer and Comanor 2007)[87]. Price manipulation as a strategic tool may be restricted in price-controlled markets that prohibit price increases. Therefore, several non-price tactics to discourage, delay, and even block generic entry have been investigated by anti-trust and competition authorities such as the DG Competition of the European Commission[88], the US Federal Trade Commission and the US Department of Justice[89].

The DG Enterprise has recently raised concerns over extension of market exclusivity through tactics including the use of patent clusters; patent related contacts/disputes and litigations; settlements with generic manufacturers that involve direct payments for later entry of the generic; launching follow-on products with only marginal improvement to displace generic medicines based on the original product; and misleading claims about the inferiority of generics (DG Competition 2009). Similar anti-competitive actions have been spotted in the US market[90].

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[86] Pearce (2005) argues that in industries that rely on innovation (pharmaceutical, semiconductor, software) three pre-expiration strategies are available to preserve market dominance after patent expiry: pre-emptive launch of a generic product; layering innovations (patenting innovations on a base product) and creating line extensions (promote revised versions of the original drugs).

[87] Frank and Salkaver (1992) develop a segmented market model with one branded producer and a competitive fringe producing the generic version and find conditions under which the branded price increases.

[88] http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/index.html

[89] http://www2.ftc.gov/bc/international/docs/genericpharma.pdf

[90] http://www.hst.org.za/news/20001207

More recently branded manufacturers have shifted from defence strategies to strategies that allow value creation from generics such as alliances with generic companies, authorized and in-house generics strategies (Scottorn 2009). Authorized generics include agreements between branded and generic manufacturers that allow generic manufacturers to produce and market the active pharmaceutical ingredient before any generic competitor enters the market. Authorized generics may block competition and dissipate the first mover advantage that grants 180-day market exclusivity provisions to the first generic entrant in the US (Peny and Covilard 2007). The branded manufacturers can avoid litigation costs and utilize their advantage in manufacturing and marketing by in-house manufacturing of generics.

Several papers in the literature have identified that licensing or partnership agreements can be used by branded firms as entry-deterring strategies in the pharmaceutical sector. It has also been demonstrated theoretically that an incumbent can deter entry by licensing its technology (Yi 1999; Kong and Seldon 2004)[91]. Mestre-Ferrandiz shows theoretically that in a market with two firms producing two branded drugs if one of the drugs goes off-patent then the originator firm has incentives to produce its generic alternative rather than allowing a third firm (competitive fringe) enter with a generic competitor (Mestre-Ferrandiz 1999). Such a strategy allows the originator to increase the price of the branded product.

Aggressive promotion (pre-patent expiry brand advertising) has also been empirically investigated as entry-deterring strategies. Evidence broadly suggests that more aggressive advertising by branded competitors is not a key strategy to deter generic entry. On the contrary, branded manufacturers prefer to reduce most promotion expenditures before patent expiry (Caves, Whinston et al. 1991; Ellison and Ellison 2007; Hurwitz and Caves October 1988). There is little potential for effective product differentiation through advertising in the generics industry as generics are equally effective copy products (Scherer 2000; Scott Morton 2000).

Grabowski and Vernon (1992) find pre-patent brand advertising to decline substantially with patent-expiry, with no significant effect on the probability of generic entry. Scott Morton (2000) examines the impact of pre-patent brand advertisement on the number of generic entrants in a market. Based on Poisson-regression estimates, she concludes that

[91] Rodrigues (2006) argues that a large-enough cross-effect between the branded and the generic equivalent a sufficient but not necessary condition for branded incumbents to blockade generic entry by marketing pseudogenerics (Rodrigues 2006)

pre-patent brand advertisement has no significant effect on the extent of generic entry and thus confirms the previous study's result. In cases where branded producers introduce new product formulations to extend market exclusivity of products that are about to lose patent protection, advertising efforts may be transferred from the original brand to the reformulation before generic entry (Huskamp and Donohue 2008).

4.2.3 Game Theoretic Models of Generic Entry/Pricing

The pioneering work belongs to Frank and Salkaver (1992) who consider a market segmentation model to characterize the behaviour of the branded producer and identify conditions under which the originator raises prices upon generic entry (Frank and Salkaver 1992). Market demand for the branded product is comprised of two components: i) Demand of consumers insensitive to generics, and ii) Demand of consumers whose decision depends on both generic and branded prices. The brand name drug behaves as a Stackelberg leader and chooses profit-maximizing price level considering the reaction of the generic manufacturers in the market. Generic entrants play a Bertrand price game taking the branded price as given. Frank and Salkaver conclude that generic entry makes the reduced-form demand of the branded producer steeper, as the most plausible proposition for the increase in branded prices following generic entry (by assumption generic entrants are competitive fringe and generic prices fall as the number of entrants increases approaching marginal cost in the limit).

Ferrandiz (1999) uses the same market segmentation approach to characterize conditions under which a branded produce has incentives to produce its own generic alternative, in a market with two branded perfect substitute goods produced by two firms (Mestre-Ferrandiz 1999). Under the market segmentation model, the branded firm has an incentive to produce its generic alternative and increase the price of its branded good.

Several theoretical papers analyze the duopoly between the branded product and the first generic within a vertical product differentiation framework (Cabrales 2003; Merino-Castelló 2003; Brekke, Königbauer et al. 2007), where vertical differentiation is defined based on perceived quality differences between the branded drug and the generic equivalent. Such differentiation is presumed to exist because of advertising efforts and goodwill stock of the branded producer, information level of the physicians and consumers about generic equivalence, sticky prescribing habits, switching costs on

the physicians and consumers' side as well as regulatory tools that promote generic use. Konigbauer (2006) analyses how price regulation affects the generic market entry decision in the presence of advertising, and shows that strict price regulation reduces the generic firms expected return from market entry and increases the likelihood that the incumbent overinvests in pre-entry advertising to deter or block generic entry (Königbauer 2007), which is in contrast to general empirical findings about advertising strategies of incumbents discussed in Section 4.2.1.

Merino-Castello (2003) and Brekke (2007) analyze the welfare effects of introducing a reference price system (Merino-Castelló 2003; Brekke, Königbauer et al. 2007). Cabrales and Merino-Castello model a two-stage game where branded and generic producers choose their "perceived" quantities in the first stage and compete in prices in the second stage. They show that under a reference pricing system branded prices decrease resulting in more intense price competition; however, market shares of generics remains constant or decreases.

Brekke et. al. (2007) consider a market with three firms: two branded drugs and a generic in the same therapeutic class. They define high- and low-type consumers that have high and low gross valuations respectively and capture vertical differentiation by deflating the gross valuation for the generic drug by a factor $\theta \in (0,1)$ (Brekke, Königbauer et al. 2007). According to their findings therapeutic reference pricing (i.e. forming reference clusters based on similar therapeutic effects) results in the most competitive market structure as expected, but at the same time reduces incentives to new drug entry. Brekke et. al. (2007) conclude that if costs of launching are not low, generic reference pricing (where clusters are defined by active ingredient) may be preferred over therapeutic reference pricing.

Mestre-Ferrandiz (2003) considers a duopoly with a branded drug and its generic alternative and compares the outcomes under a copayment system with outcomes under a reference pricing system. He identifies a profit-reducing effect of the Spanish reference pricing system for the branded and the generic producers (Mestre-Ferrandiz 2003). Mestre-Ferrandiz identifies an interval for the reference price such that prices of both the generic and branded product decrease upon the introduction of the reference price. Importantly, profits for the generics are invariably reduced compared to a copayment system if the reference price is set in this interval. The higher is the reference price, the higher is the branded price and the lower the generic price. These

findings imply that introduction of a reference price system can decrease the extent of generic entry by driving generic profits down in the equilibrium, in particular in systems where the reference price levels are lower.

Within the context of generic entry, the impact of reference pricing (RP) on branded prices and welfare has been widely studied both theoretically and empirically (López-Casasnovas and Puig-Junoy 2000). These studies broadly conclude that RP is a successful mechanism conditional on the existence of price differentials between products in the same group and a strong generic market, and that RP achieves its goals if pharmaceutical cost escalation is due to high prices rathen than excessive prescription. Firms may behave strategically to increase prices not covered by RP and recover losses in process under RP.

4.2.4 Basic Findings and Gaps in the Launch Delay Literature

A summary of the findings from the literature is presented in Table 4.1, which classifies studies by risk factors and specifies the observed effect in each study as well as markets to which the evidence belongs.

Table 4.1 Findings from the Literature on generic drug entry (and timing of generic entry)

Risk Factor	*Observed Effect*	*Evidence from*	*Author(s)*
Pre-entry market size and expected profits	Increases speed and extent of generic entry	US, UK, Germany, Spain, Sweden, Japan	Grabowski, Vernon 92; Scott Morton 99, 00; Reiffen and Ward 05; Saha 06; Moreno-Torres 09; Appelt 09; Iizuka 09
Firm Characteristics	Economies of scope (entry in several markets; number of form strengths for a given molecule)	US, Japan	Bae 97; Scott Morton 99; Iizuka 09
Drug characteristics	• Drugs for chronic conditions exhibit a higher entry rate • Entry dynamics depend on Therapeutic Class	US, Japan	Bae 97; Scott Morton 00; Saha, Grabowski 06; Iizuka 09
Price regulation/ Reimbursement	• Reference pricing restrains generic entry by reducing generic profits (the empirical evidence is weak however) • Higher price premium for branded drugs over generics increases generic share	Spain, Sweden US	Moreno-Torres 09; Ekelund 01; Konigbauer 06; Rudholm 01; Danzon & Chao 00 Hurwitz, Caves 88
Competition/ Market structure	Slower if market is highly competitive (importance of generic vs. branded competition is market-dependent) • Number of generic incumbents negatively affects extent of entry in Spain • Impact of branded competition is not clear [US and Japanese evidence suggests slower entry with increasing number of competitor molecules; Magazzini (2004) finds counter evidence]	Spain, Japan; France, Germany, UK, US	Iizuka 09; Moreno-Torres 09; Saha 06; Bae 97; Scott Morton 00; Magazzini 04
Proportion of hospital sales	Market Dependent. Increases generic entry in the US but not in Japan; a study on France, Germany, UK,	US, Japan; France,	Iizuka 09; Scott Morton 00; Magazzini 04

	and US indicates size of hospital sales has negative impact on generic shares	Germany, UK	
Branded firm strategies	Partnerships and agreements deter entry	US, Canada	Hollis 03; Reiffen 05; Berndt et al. 07; Reiffen 07
Goodwill Stock of the Branded Product	• More entrants if patent protection period is shorter	Sweden	Rudholm 01
	Mixed Evidence regarding Pre-Patent Expiry Brand Advertising • Higher promotion during patent exclusivity preserves brand shares (brand loyalty)	US	Hurwitz, Caves 88
	• Pre-patent advertising declines with patent expiry; no significant effect on generic entry	US	Caves, Whinston 91; Grabwoski, Vernon 92; Ellison, Ellison 07
	Advertising in the Generic Industry • Not effective since little potential for differentiation	US	Scherer 00; Scott-Morton 00

4.2.4.1 Gaps in the Literature

The majority of the evidence regarding generic entry belongs to the North American market; there is a paucity of evidence from the major regulated markets within the OECD. Some evidence from the Spanish and Swedish market accounts for the impact of regulation on generic entry; there is, however, no comprehensive comparative study that looks at dynamic entry across a variety of markets with different pricing mechanisms for generics. The majority of the studies have focused on the extent of generic entry rather than the timing of generic adoption. The literature offers very limited evidence on determinants of generic entry lags across markets with different pricing mechanisms. From a policy perspective both timely generic entry and fast generic uptake for a given molecule is important for cost-saving. This chapter aims to provide the first comparative analysis of generic adoption across 20 markets in the OECD by incorporating local expected generic price, extent of generic penetration, concentration of the generic sector in each market[92], firm and molecule heterogeneity.

Previous studies have used pre-entry market size and expected profits by using the sales of branded products for the given molecule, ignoring the extent of potential market penetration by generics. The literature on reference pricing clearly indicates that if branded prices are driven close to reference prices, the gap between branded and generic prices narrows which may reduce incentives for generic entry unless strong demand-side incentives are employed contemporaneously. This suggests that the impact of regulation in the context of generic entry can be proxied by relative branded-generic prices. As mentioned in Chapter 3, studies that control for regulation through prices are limited, both in the context of timing of launch of new molecules and generic copies. This study aims to close this gap by incorporating local expected generic price information as well as relative branded-generic prices in the country. In addition, this chapter will consider the extent of generic penetration in each market to estimate the expected generic market size.

Studies investigating determinants of generic entry have estimated the impact of competition using the number of branded and generic competitors. Findings in Chapter 3 demonstrated that concentration index at the therapeutic level is a significant

[92] The country set in alphabetical order is: Australia, Austria, Belgium, Canada, Finland, France, Germany, Greece, Italy, Japan, Netherlands, Poland, Portugal, South Africa, Spain, Sweden, Switzerland, Turkey, the UK and US (South Africa is an enhanced engagement country of the OECD).

determinant of hazard of launch for new molecules and high concentration acts as a barrier to entry. No studies have yet considered the impact of how concentrated the generic sector is on the timing of generic availability. In addition, there is a paucity of evidence regarding firm and product effects on the timing of first generic launch within the European market. The empirical analysis in this chapter will investigate whether there is significant heterogeneity with respect to launching firms and molecules in the availability of first generic products.

4.2.4.2 Research Questions

This chapter aims to contribute to the literature by addressing the following research questions:

- How do expected generic prices and profits affect timing of first generic entry?
- How does timing of first generic entry depend on potential competition in the local market and competition at the therapeutic class level?
- How do firm and molecule characteristics affect timing of generic product launch?

More detailed hypotheses tested in this chapter are presened in Table 4.3 in Section 4.3.4.

4.3 METHODS

4.3.1 Data

IMS data used in the study contains quarterly MIDAS sales data for the period 1999 Q1 – 2008 Q3. MIDAS is a database that combines information from IMS Health's detailed audits of retail pharmacy sales. The data covers 19 major pharmaceutical markets in the OECD and South Africa and includes USD ($) and standard unit (SU) sales for each product by quarter, molecule name, IMS generic and license status classification, global and local launch dates, pharmaceutical form, therapeutic class (ATC4), and breakdown of sales by the distribution channel. Launch in Spain, Turkey, Belgium, Greece, Portugal, Spain, South Africa represents launch in the retail sector; for Sweden launch could be either in the retail or hospital sector. Launch in the US market could be in the

retail sector (drugstores, foodstores and mail service) or non-retail sector (clinics, federal facilities, HMOs, home health care, long term care, non-federal hospitals and other miscellaneous channels)[93].

The ex-manufacturer price level for molecules is calculated by dividing the ex-manufacturer retail USD sales by volume in SU. Marketing discounts and margins along the distribution chain are ignored. The unit of analysis is molecule-country pairs. Once the generic version of a given molecule launches in one of the twenty markets, the remaining countries get under risk for the launch of the first generic version of the same molecule. This definition allows analyzing differentials in relative adoption speed with reference to the first global generic availability. This choice of risk onset cannot differentiate if the protection period has expired in individual markets, and therefore, is not an absolute measure of post-expiry delay but relative delay with respect to availability in other markets. However, all regressions control for the delay of the originator entry following the first global launch of the new molecule.

Failure time for the first generic product of molecule *j*-country *k* pair is defined as the difference between the first global generic launch date of molecule *j* and the local launch date of the generic in country *k*. Missing launch dates are approximated by period of first positive sales for those molecules that had the first generic launch after the first quarter of 1999. The number of generic molecules that launched in each market by period is presented in Table D.2 (Appendix D.1), and the distribution of the number of countries where molecules in the data have launched is presented in Figure D.1, Appendix D.

The molecule set in the IMS database is restricted to include molecules that have launched a generic in both the UK and US in order to reduce potential bias due to exclusively one-market molecules. To account for different dynamics in the pharmaceutical sector after the establishment of a single European market in 1993, the molecule set is further restricted to account for launches that occur after 1993. The analysis considers only plain molecules and ignores combination molecules composed of several active ingredients. In addition, molecules in ATC1 classes P (parasitics) and V (various drugs), anti-acne soaps, skin lotions, medicated shampoos, cleansing agents,

[93] Sales figures in USD dollars were deflated by IMF GDP deflators for each country-year using 2000 as the base year (see the Appendix for GDP deflators). Observations with negative sales, which represent products that have been returned to the manufacturer after the product has been withdrawn from the market, were dropped (about 5% of total observations).

mouth washes/rinses and contact lens solutions have been excluded. With all these restrictions, the total number of molecules analyzed is 349.

The dataset is expanded such that for each molecule-country pair there exists 117 months (from January 1999 till September 2008). Discrete time intervals are defined in months because failure times (launch dates) are interval-censored monthly. For the discrete time implementation of survival analysis each period is indexed sequentially following the onset of risk (first global launch date of the generic copy) and ends when the subject fails or is censored.

4.3.2 Model

Entry of first generic product in a given country is considered as a binary-outcome model defined as unity if entry occurs at time t and zero otherwise. The first generic alternative of molecule j launches in country k if expected profits are positive. Let Π_{jkt} represent the discounted post-entry profits for the generic of molecule j in country k. The entry decision d_{jkt} observed at time t is:

$$d_{jkt} = \begin{cases} 1 & \text{if } \Pi_{jkt} > 0 \text{ and } d_{jkn} = 0, \text{for all } n \leq t\text{-}1 \\ 0 & \text{otherwise} \end{cases}$$

The profit Π_{jkt} depends on the discounted future revenue stream net of entry costs and potential spillovers to markets that reference market k for generic price setting. The discounted future profit stream at time t ignoring marginal costs can be expressed as:

$$\Pi_{jkt} = \sum_{l=1}^{LT_{jk}} \delta^{l} \left\{ P_{jkl} \cdot Q_{jkl} - \sum_{r \neq k} L_{jkrl} \right\} - E_{jkt} + \nu_{jkt} \text{, where}$$

P is the expected generic price. Q is the expected market size for the generic alternatives of molecule j in country k; E is the fixed cost of entry; LT is the expected life-time of the generic product in the destination market; δ is the discount factor and L is the extent of price spillover to market r due to external price referencing.

The expected price P is a function of branded price levels in the local market and branded-generic price mark-up which is a function of regulation and competition in the therapeutic subgroup. In markets such as the US generic prices are determined freely but face significant price competition upon the entry of follow-on generics. In the EU,

on the other hand, generic prices are regulated in the majority of the countries (83% of European countries). Generic medicine prices can be set as a percentage below the originator price level, as the average of a selected number of European countries or as a combination of both. Also, in markets with reference pricing, regulators set a common reimbursement level for a group of interchangeable medicines, which may constitute a barrier for further price competition beyond those imposed by regulation (Dylst and Simoens 2010).

The expected market size Q depends on total sales of the branded drug and the percentage of generic penetration in the given market. Penetration of generic medicines is more successful in countries with free pricing than in countries with price regulation. Higher medicine prices achieved under free pricing facilitate market entry of generics (Schulz 2004; Martikainen, Kivi et al. 2005). In price controlled countries, regulation drives down the price of the originator medicine discouraging market entry of generics. Also, the price difference between originators and generics tends to be higher in free-priced countries, which results in higher incentives to switch to generic alternatives. Molecule's therapeutic importance affects braned sales, and hence, increases incentives to entry. Generic firms compete based on price, hence any cost reducing scale effects will provide competitive edge.

Appendix D.3 considers the two-stage price-setting game between the branded producer as a Stackelberg leader and N identical generic entrants. The subgame perfect Nash equilibrium is found by backward induction to characterize how generic prices depend on the level of branded price, the number of generic competitors and costs of entry. In the second stage, the generic manufacturers assume the branded price level as given and determine their optimum response function. In the first stage of the game, the branded producer sets the optimum branded price by using the response function of the geneircs found in the second stage. Findings from the equilibrium indicate that equilibrium generic price increases in the branded price set at the first stage and decrease in the expected number of generic competitors. Equilibrium profits of generic manufacturers are decreasing in fixed costs of entry and the marginal cost of production.

Let $\mathbf{R}, \mathbf{C}, \mathbf{M}$, and $\mathbf{F}$ be row vectors of regulation, market size and competition, molecule, firm characteristics respectively, where $\mathbf{R}$ includes price P, cost of entry E, and the size of the loss L; $\mathbf{C}$ includes expected market size Q, a priori expectations for the number of generic competitiors and the concentration index of generic competitors

in the same therapeutic group; **M** and **F** capture heterogeneity in molecule and firm characters respectively. Using these vectors the additive reduced-form profit function can be specified as:

$$\Pi_{jkt} = \mathbf{R}_{jkt}\boldsymbol{\beta}_R + \mathbf{C}_{jkt}\boldsymbol{\beta}_C + \mathbf{M}_{jk|t}\boldsymbol{\beta}_M + \mathbf{F}_{jk|t}\boldsymbol{\beta}_F + \gamma_t + u_{jkt} = \mathbf{z}_{jkt}\boldsymbol{\beta} + \gamma_t + u_{jkt}, \text{ whe}$$

re $\boldsymbol{\beta}_R$, $\boldsymbol{\beta}_C$, $\boldsymbol{\beta}_M$, and $\boldsymbol{\beta}_F$ represent corresponding column vectors of parameters to be estimated. γ_t is a function of time since global launch t of molecule j and u_{jkt} is a random error term.. Let $\mathbf{z}_{jk}(t)$ be a $1 \times p$ matrix defined as:

$$\mathbf{z}_{jkt} = \left[\mathbf{R}_{jkt}, \mathbf{C}_{jkt}, \mathbf{M}_{jkt}, \mathbf{F}_{jkt}\right].$$

Given that launch has not occurred up to time interval t, the conditional probability of launch during interval t, i.e. the interval hazard rate is:

$$\Pr(d_{jkt} = 1 \mid T_{jk} \geq t) = h_{jk}(t) = \Pr(\Pi_{jkt} > 0)$$

$$= \Pr\left(\mathbf{R}_{jkt}\boldsymbol{\beta}_R + \mathbf{C}_{jkt}\boldsymbol{\beta}_C + \mathbf{M}_{jk|t}\boldsymbol{\beta}_M + \mathbf{F}_{jk|t}\boldsymbol{\beta}_F + \gamma_t + u_{jkt} > 0\right)$$

$$= \Pr\left(\mathbf{z}_{jkt}\boldsymbol{\beta} + \gamma_t + u_{jkt} > 0\right)$$

$$h_{jk}(t) = \Pr\left(u_{jkt} > -\mathbf{z}_{jkt}\boldsymbol{\beta} - \gamma_t\right) = 1 - F\left(-\mathbf{z}_{jkt}\boldsymbol{\beta} - \gamma_t\right) = F\left(\mathbf{z}_{jkt}\boldsymbol{\beta} + \gamma_t\right),$$

where $F(.)$ is the cumulative distribution function of u and T_{jk} is the launch time of molecule j in country k. For the cloglog model $F(\mathbf{z}_{jkt}\boldsymbol{\beta} + \gamma_t) = 1 - \exp\left\{-\exp(\mathbf{z}_{jkt}\boldsymbol{\beta} + \gamma_t)\right\}$ and thus the hazard rate can be defined as:

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

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

The discrete time failure analysis again assumes two different duration specifications: i) a parametric specification $\gamma_t = \gamma_1 t + \gamma_2 t^2$; and ii) a semi-parametric specification that includes dummies for each month following risk onset, i.e. first global generic adoption.

Based on statistically more robust outcomes for cloglog regression in the previous chapter this chapter estimates parameters using cloglog regression. The binary outcome model *logit* is used as a robustness check. Using the logistic cumulative function the hazard is parameterized as follows:

$$h_{jk}(t) = \frac{1}{\left[1+\exp(-(\mathbf{z}_{jkt}\boldsymbol{\beta}+\gamma_t))\right]}, \qquad [4.6]$$

where γ_t is the vector of duration dependence. Transforming the hazard using a logit link function gives the following discrete-time logistic hazard regression model (Xie, McHugo et al. 2003):

$$\ln\left(\frac{h}{1-h}\right) = \mathbf{z}_{jkt}\boldsymbol{\beta}+\gamma_t .$$

The marginal effect has the same sign as the parameter estimate both in the cloglog and logit models. For small hazard values, cloglog and logit regressions for discrete survival analysis yield similar estimates. However, in general the estimated coefficients in the logit model will be larger than the coefficient estimates in the cloglog model (Abbott 1985). The logit model has the proportional odd assumption; as such it might be the appropriate model if the proportional odd assumption is correct in instances when the hazard rates are not "small" (see Appendix D.1). A second issue is the appropriateness of the duration-dependence specification for the baseline hazards. To avoid potential bias due to incorrect specification of the baseline hazard as a quadratic in months since risk onset, I also estimate the models assuming a non-parametric duration-dependence by including dummies for each month.

4.3.3 Variables

As in the previous chapter generic firm's entry decision and timing of entry is estimated controlling for factors both in the external and internal firm environment. External environment variables control for regulation (through expected generic prices, dummies for reference pricing and generic substitution) and expected market size; while the internal environment variables control for firm's economies of scale/scope and characteristics of the molecule. The definitions of the variables and summary statistics are provided in Table 4.2.

4.3.3.1 Regulation: Expected Generic Prices

Regulatory complexity and diversity is captured through expected generic prices of the launching molecule. This approach has not been used before for the analysis of generic launch timing, and is a natural extension of the recent studies that use price information to measure the impact of regulation on the timing of new patent-protected molecules. As lower prices squeeze the market for generics, it is expected that higher generic prices will increase hazard of launch, controlling for market size and structure as well as firm and product characteristics.

When the first generic is about to enter the market, there are no generic products for the same active ingredient. The prices of non-generic products define the maximum price limit for generic versions which are commodity products that compete based on price. In addition, regulations in some countries may require that generic prices are lower than branded products by a certain percentage (i.e. 30-35%). The expected generic price is, therefore, proxied by the product of the average branded price of the launching molecule and the median generic-branded price ratio in the local market. The average non-generic product prices in each country for the same molecule are calculated by using volume (in SU) as weights.

Generic/Non-generic Price Ratios

Several studies have identified that the market share captured by generics depends on the relative prices of the generic and originator product. Anis (2003) uses the generic-branded price ratio, *Pg/Pb*, as a measure of how regulation affects generic prices and competitiveness (Anis, Guh et al. 2003). Aronsson (2001) also finds that the price of the originator drug relative to the average price of the generic substitutes significantly affects the changes in the market share of the originator(Aronsson, Bergman et al. 2001). This ratio (*Pg/Pb*) is observed to decrease significantly over time as new generics enter the market (Caves, Whinston et al. 1991; Grabowski and Vernon 1992).

In the context of branded-generic competition, an alternative ratio that has been used to explain the market share captured by generics is $\left(P_b - P_g\right)/P_b$, where P_b and P_g are generic and branded wholesale prices for prescription drugs. Hurwitz and Caves (1988) observe that the originator's market share is decreasing in the ratio of $\left(P_b - P_g\right)/P_b$,

which they interpret as the proportional price discount offered by generic competitors (Hurwitz and Caves October 1988). I mainly use the ratio $R = P_g / P_b$ to calculate directly the expected generic price as $E(P_g) = \bar{P}_b \cdot \tilde{R}$, where $\bar{P}_b$ is the average branded price of the molecule and $\tilde{R}$ is the median ratio of $\left(P_{g_i} / P_{b_i}\right)$ across different molecules i that have a generic competitor in the destination market of launch.

Alternatively, expected generic prices could be controlled for using the average generic prices for the patent-expired molecules in the same therapeutic class (ATC4 group) since different molecules in the same ATC4 chemical group are the most imminent competitors. In some countries reference groups are defined at the chemical subgroup (ATC4 level) or even at the higher pharmacological level ATC3, which implies that average generic prices at the ATC4 level proxy expected prices either due to reference pricing or impact of competition at the chemical subgroup level. This proxy would ignore the first in class generic products for each therapeutic subgroup and further restrict the number of observations

Regulatory Dummies

Dummies for the existence of a reference price system (RPS) and generic substitution (GenSubst) are used as an additional control for the impact of regulation. Although testing the sign of these variables gives an idea of their impact on relative speed of entry for the first generic, there is considerable uncertainty regarding these measures.

Each country employs different criteria to set the reference groups and reference prices. The European Generic Association's survey of generic markets has shown that 71% of European countries use reference pricing (RP) as a tool to control the reimbursement level of medicines (Perry 2006). The reference groups can be defined at three different levels: 1) the active ingredient (e.g. Belgium, France, Italy and Portugal); 2) pharmacological class (e.g. in Poland); 3) therapeutic subgroup (e.g., Germany and Netherlands). The reference price can be set at the price of the cheapest generic (e.g. Italy and Poland); at the median price of all medicines in the group (e.g. Netherlands); highest price of available generic medicines (e.g. Portugal) (Simoens and de Coster 2006). Reference price systems (RPS) may not aid generic penetration if the prices of the originators are reduced to the reference price levels. On the other hand, RPS are

successful in generic promotion in markets where medicine prices and the price difference between generics and branded drugs are high.

Similarly, generic substitution is mandatory in some countries whereas it is promoted in others, and the incentives for substitution at the pharmacist level vary greatly across countries. For example, pharmacists' remuneration in Portugal and Spain is set as a fixed percentage of the public prices; whereas the percentage remuneration decreases as prices increase in Italy and Poland. In France and Belgium the absolute pharmacist margin is the same for originators and generics. Some countries such as Netherlands reward pharmacists for substitution by medicines priced below the reference price by allowing them to retain one-third of the price difference between the medicine dispensed and the reference price level. In France, pharmacists can obtain higher discounts for generic medicines, which increases generic substitution levels by pharmacists with the discount benefits being captured by the pharmacist. Another demand-side factor that may increase generic take-up are patient co-payments; in particular, for price sensitive segments co-payments should stimulate generic medicine use unless the co-payments are covered by private insurances as in France (Simoens and de Coster 2006).

Due to the significant heterogeneity in the definition of RPS and generic substitution incentives, the impact of regulation will be measured mainly through its effect on prices. The estimates for RPS and generic substitution, however, are presented in the Robustness Checks section.

4.3.3.2 Expected Market Size

There is little conceptual literature on determinants of timing of generic entry. Findings from the empirical literature on entry suggest that expected profits is an important determinant of entry and delays in entry. The likelihood of generic launch increases and lags in delay are reduced if the expected market size is bigger. Potential profits are a function of the branded molecule sales prior to patent expiry and the share that can be captured by generics post-patent expiry. Generics have lower profit margins compared to non-generic branded products; therefore, market success of generics depends on capturing a high share from non-generic sales.

The expected generic market size is proxed by the product of total molecule sales prior to generic entry and the average market share captured by generics (calculated over all

molecules with generic competition in individual markets). In addition, I test for the significance of market size in volume units (SU) by using the product of total molecule sales in SU and the average share of SUs captured by generics. Previous studies investigate market size in USD ($) units. Since capturing a high volume plays a critical role in the generic sector due to intense price competition, market size in USD ($) and SUs are both expected to increase the probability of quicker launch for generic products.

4.3.3.3 Market Structure and Competition

Post-entry competition is one of the most influential factors other than regulation that restricts potential profits for would-be entrants. One of the strongest signals for extensive competition following entry is the number of generic firms active in each country prior to entry. Once manufacturing infrastructure is established, the marginal cost of producing generic drugs is relatively low and switching to another molecule is relatively easy (except for certain formulations that are difficult to manufacture). Therefore, each firm that already has generic sales in the country is a potential competitor. In particular, if incumbent generic firms in the local market have prior experience with the same form, probability of launching a same-form generic might be higher (Scott Morton 1999). Complex formulations (e.g. injectables) may offer a degree of barrier to entry and better margins for generics (Karwal 2006). Ideally, potential competitors should be defined according to past experience with the same formulation. However, since generics are aggregated for the same molecule, irrespective of the form, the number of generic manufactures in the country is used as a primary proxy measure for potential competition.

Table 4.2 Variable Definitions, Descriptions and Descriptive Statistics

Expected Price	**Description**	**Level**	**N**	**mean**	**sd**	**min**	**max**
ln_Pb	Log of NonGeneric Retail Price of the Molecule	Ctry-Mol-Qrt	521376	0.147	2.10	-7.055	7.739
LMAvg_Pb	Log of Moving Average of NonGeneric Retail Price of the Molecule	Ctry-Mol-Qrt	462450	0.138	2.10	-5.622	7.714
medRatioPgPb	Expected Price Ratio Pgen/Pnongen	Ctry-Qrt	614538	0.765	0.15	0.220	1.035
LMAvgExpPg	Log Moving Average of Expected Generic Price [Log Pb * medRatioPgPb]	Ctry-Mol-Qrt	462450	-0.158	2.09	-5.796	7.458
ln_ExpPg	Log Expected Generic Price [Log Pb*medRatioPgPb]	Ctry-Mol-Qrt	521376	-0.148	2.09	-7.273	7.550
RPS	Dummy for Reference Pricing System	Ctry-Qrt	816660	0.551	0.50	0	1
GenSubst	Dummy for Generic Substitution	Ctry-Qrt	775827	0.677	0.47	0	1
Market Size	**Description**	**Level**	**N**	**mean**	**sd**	**min**	**max**
LMAvg_USD_molCtr_	Log Moving Average of Molecule Sales in the Country ($)	Ctry-Mol-Qrt	525018	6.152	2.74	-7.012	14.407
LMAvg_SU_molCtr_	Log Moving Average of Molecule Sales in the Country (SU)	Ctry-Mol-Qrt	525057	6.068	3.31	-6.908	13.789
ln_USD_moleculeCtry_i	Log Molecule Sales in the Country ($)	Ctry-Mol-Qrt	590559	6.076	2.82	-7.650	14.412
ln_SU_moleculeCtry_i	Log Molecule Sales in the Country (SU)	Ctry-Mol-Qrt	590622	5.981	3.39	-6.908	13.886
MAvg_avgGenShare_SU_	Moving Average Generic ($) Share	Ctry-Qrt	795720	42.958	13.59	9.015	76.976
MAvg_avgGenShare_USD_	Moving Average Generic (SU) Share	Ctry-Qrt	795720	38.502	12.08	6.668	63.715
avgGenShare_USD_	Average Generic ($) Share	Ctry-Qrt	816660	38.526	12.10	6.614	64.023
avgGenShare_SU_	Average Generic (SU) Share	Ctry-Qrt	816660	42.980	13.62	8.945	77.041
ExpMarketSizeSU	Expected Market Size (SU)	Ctry-Mol-Qrt	525057	9.795	3.34	-3.715	18.028
ExpMarketSizeUSD	Expected Market Size ($) [Log MAvg_USD_molCtr * avgGenShare_USD]	Ctry-Mol-Qrt	525018	9.764	2.76	-3.911	18.507

Competition	Description	Level	N	mean	sd	min	max
NumbMolCtryAtc4_	Number of Molecules in the ATC4 category (number of substitute molecules)	Ctry-Qrt-Atc4	296010	10.040	10.60	0	191
NumbMolCtryRETAtc4_	Number of Molecules in the ATC4 category (in the retail sector only)	Ctry-Qrt-Atc4	294606	9.568	10.38	0	186
NumGenFirm	Number of Generic Firms in the Country	Ctry-Qrt	816660	143.78	77.37	47	380
NumGenFirmMed	Number of Generic Firms in the Country/Median	Ctry-Qrt	816660	1.188	0.64	0.388	3.140
firmSqMed	Squared number of generic firms in the Ctr/Median of Firms squared	Ctry-Qrt	816660	1.821	2.20	0.151	9.863
IHH_gen	Herfindahl Index for Generic Sector	Ctry-Mol-Qrt	296010	4151.8	4056.63	0	10000
norm_IHH_gen	normalized Herfindahl index for generic sector: (IHH_gen-mean)/std dev	Ctry-Mol-Qrt	296010	0	1	-1.023	1.442
Molecule	**Description**	**Level**	**N**	**mean**	**sd**	**min**	**max**
MolGlobalReach	Number of Markets the molecule has launched in	Mol	816660	16.779	4.242	2	20
ln_MolGlobalUSDAnnual_	Log Annual Molecule Sales ($)	Mol-Year	811260	11.535	2.277	-4.881	16.279
ln_MolGlobalUSDMedian_	Log Molecule Sales ($) [median of annual sales over 1999-2008]	Mol	816660	11.606	2.222	2.908	16.023
ln_lag_yrs	Lag Years of the Branded Version (Local Launch - Global Launch Date)	Mol-Ctry	602316	1.279	1.256	-2.554	4.681
PercRetailUSD_	Percentage Retail Sales ($)	Ctry-Mol-Qrt	388461	71.843	37.543	0	100
Firm	**Description**	**Level**	**N**	**mean**	**sd**	**min**	**max**
lnLocalCorpSales	Log Local Sales of the Firm	Firm-Cty-Qrt	287133	9.690	2.474	-7.078	15.762
ln_globalFirmSales	Log Global Sales of the Firm	Firm-Qrt	289110	12.186	3.041	-7.078	16.225
CorpGlobalReach	Number of Markets in which the firm has sales	Firm-Qrt	293319	11.837	7.578	0	20
FirmMolDivAtT_	Firm's number of molecules	Firm-Qrt	291291	375.761	310.072	1	1112

The number of firms directly affects expected profits through its impact on prices. As the number of generic competitors increases, price competition intensifies, generic-branded price ratio decreases and the reference price is pushed down; this further decreases generic prices and profits. According to Reiffen and Ward (2005) eight or more generic entries result in near-competitive generic prices (Reiffen and Ward 2005). In the US, it has been shown that generic prices are driven down to marginal costs within a few months once the number of generic competitors is between 10 and 20 (Saha, Grabowski et al. 2006).

The number of firms in the whole market is an aggregate measure of generic sector competition in the whole market and does not account for competition at the therapeutic class level. I use the number of competitor molecules in the ATC4 subgroup (defined quarterly) as an alternative measure of competition in the robustness checks to account for the closest possible therapeutic substitution effects. A limitation of this variable is that it cannot differentiate between degrees of substitutability across active ingredients in the same ATC4 and does not incorporate possible substitution from molecules in the same pharmacologic group (ATC3)[94].

Finally, for each therapeutic subgroup (ATC4) the Herfindahl-Hirschman Index (*IHH*) is calculated as the sum of squared market shares of individual generic firms. The advantage of controlling for *IHH* is that *IHH* takes into account the relative firm size and the distribution of sales across firms. The *IHH* is small when there are numerous firms of comparatively equal sizes whereas the *IHH* increases as the number of firms in the market gets smaller and the disparity between firm sizes increases. Therefore, a high *IHH* value is an indication of little potential competition in the generic sector and that the first entrant can capture a relatively firm share from the potential market. *IHH* at ATC4 level captures the heterogeneity in competitive landscapes across different therapeutic categories.

4.3.3.4 Firm-level

Generic firms attain competitive advantage in a given market through cost competition within a given market. In a fierce price-competition environment, lower costs result in higher profit margins. The pressure for lower costs is rising due to increasing

[94] In the context of generic entry, a more refined proxy can be defined in terms of the number of molecules with existing generic competition in the same ATC4 subgroup.

globalization of generic firms, especially generic manufacturers from emerging markets such as India and China. Economies of scale and scope, therefore, might be important factors that give competitive edge to generic manufacturers as evidenced by the increasing mergers and acquisitions and vertical integration in the generics sector (Karwal 2006).

According to Karwal (2006) geographical diversification spreads out business and regulatory risks across markets, which reduces business volatility. In addition, scale economies or higher firm size reduce the financial risks associated with litigation and launch risk. Firm volatility is decreased for firms that produce a variety of products whose patent protection has expired.

Economies of scope in the pharmaceutical industry exist when it is more efficient to carry out different R&D projects by one firm rather than several different firms because knowledge can be pooled and physical assets can be shared across different R&D projects. The impact of scope effects is expected to be less important in the generic sector compared to the branded sector which incurs substantially higher R&D costs. Economies of scope are proxied by the number of molecules launched by each firm[95]. Additional heterogeneity in scale of firms is controlled for by quarterly local and global firm sales, and global reach of the firm proxied by the number of markets in which the firm has sales (across the 20 countries in the dataset).

4.3.3.5 Molecule Characteristics

As mentioned in the previous chapter, therapeutically more important molecules diffuse internationally quicker and to a wider set of markets as branded-branded competition in the pharmaceutical sector is based on quality defined by the therapeutic benefits it offers over existing competing molecules. I hypothesize that the same effect is observed for generic drugs. Therapeutically important molecules offer higher profit potential to generic manufacturers because they can capture higher price mark-ups compared to molecules of lower qulity and a higher market share that increases the ex-ante expectation for generic manufacturers. Following the approach in the previous chapter, the global reach of the originator molecule (the total number of markets to which the molecule has diffused) is used a proxy for relative therapeutic importance. Heterogeneity across molecules is also captured by total annual sales of the molecule

[95] Returns to scope could be defined at the therapeutic level and/or firm level.

(USD$) in the twenty markets, which changes on a yearly basis. To define an aggregate sales measure, in some specifications I include the median of annual global sales (USD$) during 1999-2008.

The empirical literature suggests that brand loyalty may play a role in decisions regarding generic launch. Brand loyalty depends on the duration of patent exclusivity as well as promotion efforts of the originator firm when the molecule is still under protection. The evidence, however, is mixed. Rudholm (2001) finds that a longer monopoly period reduces entry whereas Grabowski and Vernon (1992) found no significant effect of patent protection duration. Due to lack of information about protection expiry dates of molecules, this study cannot directly control for the exclusivity period in the market. However, launch delays (time elapse between the first global launch date and local launch date) of originator products are used as a control for the monopoly period loss in each market. The higher the delay, the shorter is the period available for building brand loyalty[96].

Finally, the literature suggests that the share of hospital vs. retail sales also has implications for the extent of generic entry (but no evidence exists on timing of entry conditional on entry in the EU5). For example, Scott Morton (2000) finds a positive relationship between the share of hospital sales and the entry of generic products due to institutional factors that facilitate generic entry in the hospital sector. On the other hand, Magazzini (2004) finds evidence to the contrary that the size of the hospital sector has a negative impact on generic market share in USA, UK, Germany, and France[97].

4.3.4 Hypotheses

Based on economic theory and findings from the literature, the empirical analysis will test the following main hypotheses for drivers of launch timing in the generic sector:

[96] As the empirical results of the previous chapter showed, launch delays of the original molecule is strongly associated with price-controlled markets, and therefore, partially captures regulation effects in each market

[97] For US retail sales are composed of foodstores, drugstores and mail service. For Sweden sales are combined so percentage retail sales are not known. Belgium, Greece, Portugal, South Africa, Spain and Turkey have retail only sales. Remaining markets that have both hospital and retail sales are Australia, Austria, Canada, Finland, France, Germany, Italy, Japan, Netherlands, Poland, Switzerland, and the UK.

Table 4.3 Hypotheses for the key drivers of launch timing in the generic sector

Factor	*Testable Hypotheses*	*Evidence from the Literature*	*Expected Sign of the Coefficient*
Regulation	H1 a.1: High expected generic prices increase the hazard rate (decrease launch lag) for generic products	No direct empirical evidence	+ Price Coefficient (Higher generic prices, controlling for other factors, increase expected revenue and profitability for generic manufacturers)
	H1 a.2: Higher branded prices increase the hazard of launch of generic products	Evidence exists	+ Pb Coefficient (generic prices may be directly linked to branded prices; markets with higher prices tend to have higher generic prices)
	H1 a.3: Generic-branded price ratio *Pg/Pb* negatively affects hazard of launch.	No evidence on timing of generic entry	- Pg/Pb Coefficient (Keeping branded price fixed, lower generic prices allow generics to capture a higher volume share)
Market Size	H1 b.1: The higher the branded molecule sales prior to generic launch (in $ or SU), the higher the hazard of launch	Empirical evidence exists for sales (in $) of branded products	+ Market Size Coefficient (Both the sign of SU and USD sales are expected to be positive)
	H1 b.2: The higher the expected generic market size (= branded molecule sales * the average generic share in the local market), the higher the hazard of launch	No direct empirical evidence	+ Expected Market Size Coefficient (Market size increases incentives for entry as the net present value of entry is increased)
Competition & Market Structure	H1 c.1: A higher number of expected generic competitors decreases the hazard of entry	No evidence	- Coefficient for number of competitor firms (Theoretically, I have shown that number of generic entrants has a negative impact on expected profits)
	H1 c.2: The higher the number of substitute molecules in the therapeutic class, the lower is the hazard rate	No evidence	- Coefficient for Substitute Molecules (Either reference pricing or competition will drive prices and potential profits down)

	H1 c.3: The higher the Herfindahl concentration index of generic manufacturers at the therapeutic class level, the lower the hazard rate	No evidence	- Concentration Coefficient (in Chapter 3 concentration in on-patent sector had a negative coefficient estimate. Industrial organization literature predicts that concentration reduces the equilibrium level of entry)
Molecule	H1d.1: Generic entry for therapeutically/commercially important molecules is faster	No evidence	+ Coefficient for Molecule's Global Reach and Global Sales (higher branded prices and higher profit potentials)
	H1d.2: The longer the lag for the entry of the originator molecule, the faster the generic entry	No evidence	+ Coefficient for the Lag of the Originator (longer lags imply shorter exclusivity and lower brand loyalty)
	H1d.3: Percentage of molecule sales in the retail sector increases hazard of launch	Contradictory	? (Prices in the hospital sector tend to be lower than in the retail sector but volume effect could dominate)
Firm	H1 e.1: Firm economies of scope (number of molecules in the portfolio) increase the hazard of launch	Evidence exists	+ Economies of Scope Coefficient (Economies of scope allow lower-cost entry as the firm can switch quickly and less costly from one product line to another. Also, knowledge spillovers across different product lines may further lower development and entry costs)
	H1 e.2: Firms' scale has positive effect on the hazard of launch.	Evidence from the branded sector; No firm empirical evidence exists for the generic sector	+ Coefficient for Firm's Global/Local Sales (Scale effects are expected to be less important than in on-patent sector because R&D and advertising costs are much lower compared in the generic sector. However, economies of scale may allow vertical integration in the supply chain as well as mergers with other generic manufacturers to decrease costs)
			+ Coefficient for Firm's Global Reach A wider global reach indicates potentially bigger firm size and higher familiarity with diverse regulatory environments)

4.4 EMPIRICAL RESULTS

This section estimates the hazard of first generic product launch in individual markets following the first global generic launch of the originator molecule. All regressions control for the lag of the originator molecule as well as heterogeneity in anatomic therapeutic categories and country of launch. All errors are clustered by molecule-country since there might be dependency across the errors of the same molecule-country pair. Regressions are run for molecules with first global launch after 1993, the year the European Union was legally created.

Parametric Duration Dependence Base Case Results

Table 4.4 presents the marginal effects (*dy/dx*) for molecules that had the first generic launch globally after 1993. Maximum likelihood estimation was carried out using discrete time implementation of the proportional hazard model with *complementary log log* regression and *logit* regression for robustness check. Marginal effects and coefficient estimates are very close or identical across *cloglog* and *logit* estimations[98]. Regressions presented in Table 4.4 assume parametric duration dependence of the form $h_0(t) = t + \ln(t^2)$ for the hazard function.

Base case results show that regulation proxied by expected generic prices for the launching generic product has a significant impact on the hazard of launch following the first global generic launch. This effect is robust across different model specifications and inclusion or exclusion of calendar year dummies. Marginal effects are comparable in magnitude across *cloglog* and *logit* estimates. The significance level depends on whether calendar year dummies are included or not. With no calendar year dummies the significance is at the 0.001 or 0.01 level, whereas with calendar year dummies the significance level reduces to 0.05. This could be due to the fact that calendar year dummies capture some of the variation in expected generic prices (for example, expected generic prices would reduce over time in price-controlled markets due to downward pressure on branded prices). The marginal effect of log expected generic prices on the hazard of first generic launch is on the order of 0.002.

[98] Preliminary runs with cox regression could not achieve meaningful marginal effects. Alternative estimations that assume common frailty for each molecule-country pair using *xtcloglog* had difficulty in converging due to non-concavity.

The mean of expected generic price is 21.125$/SU and the standard deviation is 86.728$/SU. Therefore, considering the average price level, an increase of one standard deviation in expected generic prices (rather than log prices) increases probability of launch by approximately 0.8% [99].

The marginal effect of log average branded prices is also 0.002. Considering the mean branded price of 28.971$/SU and standard deviation of 119.646$/SU, an increase of one standard unit increase in branded prices increases probability of launch again approximately by 0.8%[100].

Expected market size in USD is significant across all specifications. However, expected market size in SU is only significant in specifications without the calendar year dummies. The marginal effect of log expected market size for generics in USD varies from 0.002 to 0.004 depending on whether calendar year dummies are included or not. The mean of the expected market size of observations used in the regressions is 472,723.3 (USD$) with a standard deviation of 3,255,101 (USD$). An increase of one standard deviation in the expected generic market size increases hazard of launch by 1.4%-2.8%[101]. On average, an increase in market size (in USD$) by one standard unit increases probability in launch more than a corresponding increase in the expected generic price by one standard unit. It should be noted, however, that the uncertainty around the expected market size is higher. The standard deviation for expected market size is 6.8 times higher than the mean, whereas for expected generic prices the standard deviation is 4.3 higher than the mean expected prices.

The impact of the number of generic competitors in the market depends on whether calendar year dummies are included or not. When calendar year dummies are included the higher the number of competitors the lower is the hazard of launch. On the other

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99

$$(86.728)\frac{\partial y}{\partial p} = (86.728)\frac{\partial y}{\partial \ln p}\cdot\frac{\partial \ln p}{\partial p} = (86.728)\frac{\partial y}{\partial \ln p}\cdot\frac{1}{p}$$

$$= (86.728)(0.002)\frac{1}{21.125} = .008 \sim 0.8\%$$

100 $$(119.646)\frac{\partial y}{\partial \ln p_b}.\frac{1}{p_b} = (119.646)(0.002).\frac{1}{28.971} = 0.008 \sim 0.8\%$$

101 $$(3255101)\frac{\partial y}{\partial \ln MSize}.\frac{1}{MSize} = (3255101)(0.002).\frac{1}{472723.3} = 0.014 \sim 1.4\%$$

$$(3255101)\frac{\partial y}{\partial \ln MSize}.\frac{1}{MSize} = (3255101)(0.004).\frac{1}{472723.3} = 0.028 \sim 2.8\%$$

hand when calendar year dummies are excluded, number of competitors significantly increases the hazard of launch. The effect of competition is further investigated in robustness checks, Section 4.4.1.3, through alternative proxies.

Surprisingly, molecule and firm effects show no robust statistical significance. Marginal effects of global molecule sales alternate from positive to negative values. On the other hand, marginal effects of global firm sales is consistently positive across different specifications suggesting that firm scale increases the speed of launch for generic products. The effect of firm scale, however, is significant at the 0.075 level.

There is robust evidence that the hazard of launch is concave in the number of months elapsed since risk onset. The variable *sequence* indicates the number of months elapsed since the first global launch of the generic version of the originator molecule. The marginal effect of both number of months and log number of months squared since risk onset is significant at the 0.001 level. This is in line with the duration dependence in the previous chapter that analyzed the launch timing of new molecules. The probability of launch in individual countries following the first launch initially increases and then decreases.

Comparing the information criteria statistics across the models with calendar year dummies and no calendar year dummies indicates that the model with calendar year dummies has a better overall fit.

The corresponding coefficient estimates for the models in Table 4.4 are presented in Table D.4, Appendix D.2.1. The coefficient estimates for *cloglog* and *logit* are very close to each other, which suggests that the hazard of launch on average is small. As expected, in cases where the coefficients are not exactly identical, logit estimates are marginally higher than the cloglog estimates.

Table 4.4 Parametric Duration Dependence : Marginal Effects for Base Case Cloglog and Logit Estimates for First Generic Launch

Variables	*With Calendar Year Dummies*						*No Calendar Year Dummies*					
	CLOGLOG			LOGIT			CLOGLOG			LOGIT		
	1	2	3	1	2	3	1	2	3	1	2	3
Expected Generic Price												
LMAvgExpPg	0.002*	0.002*		0.002*	0.003*		0.002**	0.004***		0.002**	0.005***	
	[0.0006]	[0.0011]		[0.0007]	[0.0011]		[0.0007]	[0.0013]		[0.0007]	[0.0013]	
LMAvg_Pb			0.002*			0.002*			0.002**			0.002**
			[0.0006]			[0.0007]			[0.0007]			[0.0007]
medRatioPgPb			0.007			0.008			-0.018			-0.02
			[0.0155]			[0.0160]			[0.0190]			[0.0192]
Expected Market Size												
ExpMarketSizeUSD	0.002**			0.002**			0.004***			0.004***		
	[0.0008]			[0.0008]			[0.0010]			[0.0010]		
ExpMarketSizeSU		0.001			0.001			0.002*			0.003**	
		[0.0008]			[0.0008]			[0.0010]			[0.0010]	
LMAvg_USD_molCtr_			0.002*			0.002**			0.003***			0.003***
			[0.0008]			[0.0008]			[0.0009]			[0.0009]
avgGenShare_USD_			0.000			0			0.002***			0.002***
			[0.0003]			[0.0003]			[0.0003]			[0.0003]
Competition												
NumGenFirmMed	-0.032	-0.032	-0.031	-0.029	-0.029	-0.029	0.127***	0.131***	0.100***	0.129***	0.133***	0.101***
	[0.0175]	[0.0176]	[0.0175]	[0.0180]	[0.0180]	[0.0179]	[0.0184]	[0.0185]	[0.0169]	[0.0186]	[0.0187]	[0.0170]
Molecule Characteristics												
ln_lag_yrs	0.002*	0.002	0.002*	0.002*	0.002	0.002*	0.001	0	0.001	0.001	0	0.001
	[0.0011]	[0.0011]	[0.0011]	[0.0011]	[0.0011]	[0.0011]	[0.0012]	[0.0013]	[0.0012]	[0.0013]	[0.0013]	[0.0012]

ln_MolGlobalUSDAnnual_	-0.001	0.000	-0.001	-0.001	0	-0.001	-0.002	0	-0.001	-0.002	0	-0.001
	[0.0010]	[0.0010]	[0.0010]	[0.0010]	[0.0011]	[0.0010]	[0.0012]	[0.0012]	[0.0011]	[0.0012]	[0.0012]	[0.0011]
Firm Characteristics												
ln_globalFirmSales	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.000	0.000
	[0.0003]	[0.0003]	[0.0003]	[0.0003]	[0.0003]	[0.0003]	[0.0004]	[0.0004]	[0.0004]	[0.0004]	[0.0004]	[0.0004]
Time Since Risk Onset												
sequence	0.000***	0.000***	0.000***	0.000***	0.000***	0.000***	0.001***	0.001***	0.001***	0.001***	0.001***	0.001***
	[0.0001]	[0.0001]	[0.0001]	[0.0001]	[0.0001]	[0.0001]	[0.0001]	[0.0001]	[0.0001]	[0.0001]	[0.0001]	[0.0001]
ln_sequenceSq	-0.006***	- 0.006***	- 0.006***	- 0.006***	- 0.006***	- 0.006***	- 0.009***	- 0.009***	- 0.008***	-0.009***	-0.009***	-0.008***
	[0.0007]	[0.0007]	[0.0007]	[0.0007]	[0.0007]	[0.0007]	[0.0007]	[0.0007]	[0.0007]	[0.0008]	[0.0008]	[0.0007]
Year Dummies	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Model Stats												
Number of Observations	19698	19698	19698	19698	19698	19698	19698	19698	19698	19698	19698	19698
Log Likelihood	-2218.21	-2221.42	-2218.47	-2220.04	-2223.32	-2220.28	-2326.57	-2332.77	-2306.01	-2327.9	-2334.26	-2307.48
chi2	737.92	736.01	749.44	681.63	681.78	687.45	418.16	406.76	447.5	380.01	371.24	413.37
P value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Akaike Info Criteria	4530.422	4536.85	4534.93	4534.08	4540.65	4538.56	4731.13	4743.53	4694.02	4733.79	4746.53	4696.95
Bayesian Info Criteria	4901.17	4907.59	4921.46	4904.83	4911.4	4925.08	5038.77	5051.17	5017.44	5041.44	5054.17	5020.37

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets). Marginal effects (dy/dx) reported . Duration dependence is captured by sequence and ln_sequence, which correspond to months since risk onset and the log of squared months since risk onset, i.e. $t + \ln(t * t)$. Year, ATC1 and Country Dummies not reported.

Non-Parametric Duration Dependence Base Case Results

For robustness checks, non-parametric regressions were run with cloglog and logit specification by including dummies for each month following the risk onset and specifying *noconstant* option in Stata. This avoids prior assumptions of the parametric estimations regarding the functional form of the hazard with respect to time. Non-parametric duration dependence assumes a constant hazard rate during each monthly interval.

The coefficient estimates using non-parametric duration dependence are provided in Table D.5 (Appendix D.2.1). The signs of the coefficients are broadly in line with the parametric specification. Non-parametric estimates also suggest that launch hazard for generics is higher when expected price and market size is higher. However, the significance of price estimates with calendar year dummies included is weaker. For specifications with no calendar year dummies a lower generic-branded price ratio is negatively associated with a lower hazard rate and is statistically significant. Higher generic share in molecule sales is associated with higher hazard rates and is statistically significant.

The impact of competition, proxied by the number of generic firms, is not robust and shows the same trend as in the parametric duration specification. Launch hazard is decreasing in the number of generic firms when calendar year dummies are included and increasing if year dummies are excluded. A higher number of potential generic competitors indicates that the entrant will capture a lower share of the market and that price competition will be more intense. Therefore, the extent of potential generic competition affects the entry decision negatively.

Findings for molecule and firm effects are more robust in terms of the sign of the parameter estimates. The coefficients of therapeutic importance (global molecule sales) are positive and statistically significant in few model specifications whereas the coefficients of global firm sales (scale effect) are also positive but not statistically significant.

Akaike and Bayesian information criteria for non-parametric specifications are much higher compared to the parametric duration specifications. This can be explained by the fact that the number of estimated parameters increases considerably due to the inclusion of 117 dummies for each month (from 1999 Q1 to

2008 Q3) in the non-parametric specification, whereas the parametric specification has only 2 parameters to be estimated for duration dependence, t and $\ln\left(t^2\right)$. Parametric specifications where calendar year dummies are excluded have the lowest information criteria in general, and therefore, potentially provide a better overall fit to the data.

Multicollinearity

Before proceeding with the robustness checks for the results obtained I tested for potential issues of multicollinearity by computing the variance inflation factors (*VIF*). In particular, the change in the sign of the coefficient of *number of generic firms* depending the inclusion or exclusion of calendar dummies raises suspicions of multicollinearity. The main problem of multicollinearity is the inflation in variances of the least squares estimators of coefficients. This may result in wide swings in the parameter estimates with small changes in the data and coefficients may have the wrong sign and implausible magnitudes. A maximum *VIF* greater than 10 is thought to signal severe collinearity (Mansfield and Helms 1982; Mason and Perreault Jr 1991).

*VIF*s were calculated by first running an ordinary least squares regression and then calculating the *VIF* by the command *estat VIF* in Stata. *VIF* estimates are presented in the Appendix D.2.3 in Table D.29 and Table D.30. The variance inflation factor for the proxy of competition (number of generic firms) is 244.7 and the mean value is 16.58, which indicates a severe multicollinearity problem. When the normalized Herfindahl-Hirshman Index within therapeutic categories is used instead of the number of generic firms as a proxy for competition the multicollinearity problem subsides and the mean *VIF* reduces to 2.91. It should be noted that although the *VIF* factors for calendar year dummies is less than 10, they remain predominantly above 5, which may explain some of the sensitivity in the coefficients with respect to the inclusion or exclusion of calendar year dummies from the regressions.

Table 4.5 presents the marginal effects *dy/dx* for the same model specifications as in Table 4.4 after replacing the control for competition from number of generic firms to the normalized Herfindahl-Hirschman Index to avoid potential bias due to the high inflation factor of number of generic firms (see Table D.31 in Appendix D.2.3 for coefficient estimates). The marginal effects are slightly higher compared to the

marginal effects in Table 4.4 for specifications with no calendar year dummies. The Akaike and Bayesian information criteria indicate that models with the Herfindahl index provide a better fit overall. Therefore, the robustness checks in the following section control for competition by using the normalized Herfindahl Index at the therapeutic class level to avoid problems due to multicollinearity.

Table 4.5 Parametric Duration Dependence: Marginal Effects using Herfindahl Index as a proxy for competition

Variables	with calendar year dummies						no calendar year dummies					
	cloglog 1	cloglog 2	cloglog 3	logit 1	logit 2	logit 3	cloglog 1	cloglog 2	cloglog 3	logit 1	logit 2	logit 3
Expected Generic Price												
LMAvgExpPg	0.002***	0.003**		0.002***	0.003**		0.003***	0.005***		0.003***	0.005***	
	[0.0006]	[0.0010]		[0.0006]	[0.0010]		[0.0006]	[0.0012]		[0.0007]	[0.0012]	
LMAvg_Pb			0.002***			0.002***			0.002***			0.002***
			[0.0006]			[0.0006]			[0.0006]			[0.0006]
medRatioPgPb			0.000			0.004			-0.022			-0.022
			[0.0133]			[0.0136]			[0.0147]			[0.0151]
Expected Market Size												
ExpMarketSizeUSD	0.002*			0.002**			0.004***			0.004***		
	[0.0007]			[0.0007]			[0.0009]			[0.0009]		
ExpMarketSizeSU		0.001			0.001			0.003***			0.003***	
		[0.0007]			[0.0007]			[0.0009]			[0.0009]	
LMAvg_USD_molCtr_			0.002*			0.002**			0.003***			0.003***
			[0.0007]			[0.0008]			[0.0008]			[0.0008]
avgGenShare_USD_			0.000			0.000			0.001***			0.001***
			[0.0002]			[0.0002]			[0.0002]			[0.0002]
Competition												
norm_IHHatc4_gen	0.009***	0.009***	0.009***	0.009***	0.009***	0.009***	0.011***	0.011***	0.010***	0.011***	0.011***	0.011***
	[0.0008]	[0.0008]	[0.0008]	[0.0008]	[0.0008]	[0.0008]	[0.0009]	[0.0009]	[0.0008]	[0.0009]	[0.0009]	[0.0009]
Molecule Characteristics												
ln_MolGlobalUSDAnnual_	-0.001	0.000	-0.001	-0.001	0.000	-0.001	-0.002*	-0.001	-0.002	-0.002*	-0.001	-0.002
	[0.0009]	[0.0009]	[0.0009]	[0.0009]	[0.0009]	[0.0009]	[0.0010]	[0.0010]	[0.0010]	[0.0010]	[0.0011]	[0.0010]

ln_lag_yrs	0.001	0.001	0.001	0.001	0.001	0.001	-0.001	-0.001	-0.001	-0.001	-0.001	0
	[0.0010]	[0.0010]	[0.0010]	[0.0010]	[0.0010]	[0.0010]	[0.0011]	[0.0011]	[0.0010]	[0.0011]	[0.0011]	[0.0011]
Firm Characteristics												
ln_globalFirmSales	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	[0.0003]	[0.0003]	[0.0003]	[0.0003]	[0.0003]	[0.0003]	[0.0004]	[0.0004]	[0.0003]	[0.0004]	[0.0004]	[0.0003]
Time Since Risk Onset												
sequence	0.000***	0.000***	0.000***	0.000***	0.000***	0.000***	0.001***	0.001***	0.001***	0.001***	0.001***	0.001***
	[0.0001]	[0.0001]	[0.0001]	[0.0001]	[0.0001]	[0.0001]	[0.0001]	[0.0001]	[0.0001]	[0.0001]	[0.0001]	[0.0001]
ln_sequenceSq	-	-	-	-	-	-	-	-	-	-	-	-
	0.005***	0.005***	0.005***	0.005***	0.005***	0.005***	0.007***	0.007***	0.007***	0.008***	0.008***	0.007***
	[0.0006]	[0.0006]	[0.0005]	[0.0006]	[0.0006]	[0.0006]	[0.0006]	[0.0006]	[0.0006]	[0.0006]	[0.0006]	[0.0006]
Heterogeneity												
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calendar Year Dummies	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Model Stats												
Number of Observations	19698	19698	19698	19698	19698	19698	19698	19698	19698	19698	19698	19698
Log likelihood	-2083.37	-2086.36	-2083.47	-2082.67	-2085.94	-2082.87	-2192.41	-2199.68	-2170.06	-2194.79	-2202.22	-2172.71
chi2	798.35	798.11	817.25	668	669.02	682.63	617.43	604.45	615.58	521.4	510.85	530.79
p-value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Akaike Info Criteria	4260.73	4266.72	4264.94	4259.34	4265.87	4263.75	4462.82	4477.37	4422.13	4467.58	4482.45	4427.42
Bayesian Info Criteria	4631.48	4637.47	4651.46	4630.09	4636.62	4650.28	4770.46	4785.01	4745.55	4775.23	4790.09	4750.84

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets). Marginal effects (dy/dx) reported. Duration dependence is captured by sequence and ln_sequence, which correspond to months since risk onset and the log of squared months since risk onset, i.e. t + ln (t *t) . Year, ATC1 and Country Dummies not reported.

4.4.1 Robustness Checks

Robustness checks were carried out using the same structure as in the base case regression runs. Each model specification was estimated using both parametric and non parametric duration dependence (see Table 4.6). The parametric specifications assumed a quadratic in months elapsed since the risk onset ($t + \ln(t^2)$) and the non-parametric specifications included dummies for each month interval following global launch by suppressing the constant in the regressions. Based on differences in coefficient estimates in preliminary results, all specifications were run with and without calendar year dummies. *cloglog* and *logit* regressions were estimated to test the significance of regulation, expected market size, competition, molecule and firm characteristics by using different proxies for each category. All regressions include country and ATC1 dummies.

Table 4.6 Structure of the Robustness Regressions

Parametric Duration Dependence		Non-Parametric Duration Dependence	
With Calendar Year Dummies	No Calendar Year Dummies	With Calendar Year Dummies	No Calendar Year Dummies
Cloglog & Logit	Cloglog & Logit	Cloglog & Logit	Cloglog & Logit
Regulation	Regulation	Regulation	Regulation
Market Size	Market Size	Market Size	Market Size
Competition	Competition	Competition	Competition
Molecule	Molecule	Molecule	Molecule
Firm	Firm	Firm	Firm

4.4.1.1 Regulation

This section tests for the robustness of expected price effects using different proxies for the expected generic price and controlling for expected market size, competition, molecule and firm effects, lag of the originator molecule, country, ATC1 and calendar year effects. The expected generic price is defined as the product of average branded price and the median *Pg/Pb* ratio in the country. In addition, the significance of the reference pricing systems (RPS) and generic substitution (GenSubst) is investigated. The impact of regulation is estimated using the following variables:

- log moving average of expected generic prices over the past 4 lags (LMAvgExpPg)[102],
- lagged log expected generic prices by one quarter (L3ln_ExpPg),
- log moving average of branded prices for the launching molecule (L3ln_Pb) and median generic-branded price ratio (medRatioPgPb),
- log of expected generic prices (ln_ExpPg) and median generic-branded price ratio (medRatioPgPb),
- log moving average of expected generic prices over the past 4 lags (LMAvgExpPg) and RPS dummies
- log moving average of expected generic prices over the past 4 lags (LMAvgExpPg) and generic substitution dummies.

Lagged or moving average prices are used to avoid problems of endogeneity. The moving average approach also tests significance of price when short-term fluctuations are smoothed out to highlight longer-term trends in price. Estimates are presented in Appendix D.2, Section D.2.2.1 (see Table D.7 - Table D.10). Higher expected generic prices (average branded price of the molecule times the median generic/branded price ratio) significantly increase the hazard effect, regardless of whether lagged expected generic price or the moving average is used. Therefore, regulations that drive first generic prices down before launch are associated with longer delays. The effect is robust across *cloglog* and *logit* regressions as well as to the inclusion or exclusion of calendar year dummies. Coefficient estimates for expected generic prices are slightly higher with parametric duration dependence compared to non-parametric duration dependence estimates.

As expected, generic launch hazard is increasing in the log lagged average branded price controlling for country heterogeneity by dummies for each market. The positive impact of branded prices on generic launch is significant across all specifications. This implies that price controls that depress branded prices may have spillover effects in terms of slower generic launch. Also, in specifications where calendar year dummies are excluded, there is an indication that controlling for expected generic prices, a higher P_g / P_b ratio lowers the hazard of launch. This is consistent with the fact that generics may capture a higher share from branded sales with a lower P_g / P_b ratio which may

[102] Moving averages are defined with the weights of 0.4 for the first lag, 0.3 for the second lag, 0.2 for the third lag and 0.1 for the fourth lag.

compensate for the reduction in the generic prices. In Model 3 the coefficient for P_g / P_b is significantly negative controlling for expected generic prices. However, when calendar year dummies are included the effect of P_g / P_b is not significant over and above the effect of average branded prices or expected generic prices.

The impact of reference pricing (RPS) schemes and generic substitution is tested by dummies, on top of the effect of expected generic prices. There is significantly robust evidence that generic substitution and RPS increase the speed of first generic entry when calendar year dummies are excluded. When calendar year dummies are included, however, generic substitution significantly increases speed of generic entry only for non-parametric duration specifications, even after controlling for non-generic price levels of the launching molecule. It should be emphasized that the dummies for RPS and generic substitution do not account for the heterogeneity across countries in reference pricing and generic substitution schemes.

Generic launch is considered relative to the first generic launch date observed across the 20 countries and does not consider whether the original molecule has expired in individual markets[103]. However, all regressions control for the delay in the originator molecule. Longer delays in the launch of the originator molecules would reduce the exclusivity period and reduce the potential for brand loyalty. The literature suggests that shorter monopoly periods reduces brand loyalty and increases generic entry. In all specifications with calendar year dummies, the higher the lag of the originator molecule (i.e. the shorter the exclusivity period), the higher is the hazard of launch for the first generic product.

Finally, the interaction of time since global launch and expected generic price was tested (see Table D.11 in Appendix D.2, Section D.2.2.1). Two specifications use the lagged expected generic price and two use the moving average price[104]. Including time interaction results in positive estimates for the price effect and price-time interaction; however, neither are significant [105].

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[103] If generic launch occurs prior to patent expiry, this could be an indication of launch of an authorized generic by the originator firm to delay entry of follow-on generic competition, which I cannot control for.

[104] There was no multicollinearity problem with these specifications (VIFs for all variables is less than 10)

[105] For specifications that exclude calendar year dummies price and price-time interactions are significant at the 0.07-0.09 level. If calendar year dummies are included p-value for the expected price ise 0.13

4.4.1.2 Potential Market Size

This section tests for the robustness of market size effects (in USD$ and SUs) controlling for expected generic price, competition, molecule and firm effects, lag of the originator molecule, country, ATC1 and calendar year effects. Potential market size estimates are based on quarterly molecule sales and the percentage of shares captured by the generics. The following proxies were used to estimate the robustness of the impact of potential market size (see Appendix D.2, Section D.2.2.2, Table D.12 - Table D.15):

- Expected generic market size (in USD$) for the Molecule (ExpMarketSizeUSD): defined as the product of molecule sales in USD$ and the average generic share over molecules in the country,
- Expected generic market size (in SU) for the Molecule (ExpMarketSizeSU): defined as the product of molecule sales in SU and the average generic share over molecules in the country.

Weaker proxies that ignore generic shares include:

- Log Moving Average of Molecule sales (in USD$) in the country (LMAvg_USD_molCtr_): defined over the past 4 quarters with decreasing weights for older quarters106,
- Log Moving Average of Molecule sales (in SU) in the country (LMAvg_SU_molCtr_): defined over the past 4 quarters, with the weights being 0.4, 0.3, 0.2 and 0.1 respectively from the first lag to the fourth lag,
- Log Lagged Molecule Sales in (USD $) in the country (L3ln_USD_moleculeCtry_i),
- Log Lagged Molecule Sales in (SU) in the country (L3ln_SU_moleculeCtry_i).

Expected generic market size in USD$ is significant across all specifications and robust to the inclusion or exclusion of calendar year dummies. Expected generic market size in SUs increases hazard of launch but is significant when calendar year dummies are excluded. Significance level of market size is higher in non-parametric models (0.01 compared to 0.05 in the parametric specifications).

[106] Weights are 0.4, 0.3, 0.2 and 0.1 respectively.

4.4.1.3 Competition

This section tests for the robustness of the impact of market structure and competition on the timing of generic launch controlling for expected generic price, expected generic market size, molecule and firm effects, lag of the originator molecule, country, ATC1 and calendar year effects. Market structure is captured through the number of firms (NumGenFirmMed) and squared number of firms (firmSqMed) in the country, both divided by the median values to get meaningful standard errors. Competition at the therapeutic category level is controlled for by the number of substitute molecules in the ATC4 category (NumbMolCtryAtc4_[107]) and the normalized Herfindahl-Hirschman index for generic firms by ATC4-country and quarter (see Appendix D.2, Section D.2.2.3, Table D.16 - Table D.19).

Concentration ratio has the most robust and significant effect across different specifications. Regardless of whether regressions are estimated by *cloglog* or *logit*, parametrically or non-parametrically, the effect of concentration in the ATC4 is significant at the 0.001 level. The higher the concentration of generic firms in the therapeutic category, the higher the hazard of generic launch. This is contrary to the findings in the previous chapter where concentration coefficient had a negative coefficient. Strong generic competition at the therapeutic level, therefore, seems to be a barrier to entry for the follow-on generic products.

The effect of the number of substitute molecules in the therapeutic category is not significant and not robust across specifications. This indicates that inter-molecular competition within a therapeutic subgroup is not a significant determinant of generic entry decisions. The effect on the launch hazard is positive with calendar year dummies and negative without calendar year dummies, both for parametric and non-parametric specifications.

Similarly, the effect of the number of generic manufacturers in the market depends on whether calendar dummies are included. With calendar year dummies added, the higher the number of competitors, the lower is the hazard rate, i.e. the higher the potential generic competition, the slower is the international diffusion of generics. This can be explained by the fact that the incentives for entry are reduced as potential competition increases. The coefficient of the squared number of firms is negative in all specifications (and significant in models where calendar dummies are excluded), which

[107] NumbMolCtryRETAtc4_ tests for the number of molecules in atc4 in the retail sector only

suggests a concave relationship between the hazard of first generic launch and the number of potential competitors.

4.4.1.4 Molecule Heterogeneity

The robustness of molecule effects is tested by controlling for expected generic prices, expected market size, competition and firm effects. Proxies that capture molecule heterogeneity include:

- Global reach of the molecule (MolGlobalReach), i.e. the number of countries in which the molecule has launched,
- Annual sales (USD$) of the molecule in each country (ln_MolGlobalUSDAnnual_),
- Median sales (USD$) of the molecule during 1999 Q1 – 2008 Q3 in each country (ln_MolGlobalUSDAnnual_),
- Log years of delay for the originator to enter the local market following the global launch of the new molecule,
- Percentage of molecule sales in the retail sector (PercRetailUSD_).

Estimates for the global reach of the molecule are negative in all specifications, but are not statistically significant (see Appendix D.2, Section D.2.2.4, Table D.20 - Table D.24). Similarly, the coefficient of annual sales of the molecule is negative in parametric specifications and positive in non-parametric specifications. The effect of global molecule sales is not significant in either of the specifications. The coefficient of the median molecule sales is negative across different specifications too (except for non-parametric estimates with calendar year dummies). These estimates overall suggest that for decisions regarding generic entry the impact of molecule's importance is not statistically significant after accounting for expected price and market size effects. Local sales (expected market size), on the other hand, is significantly important. The fact that global sales of the molecule are not a significant determinant of hazard of generic launch suggests that local effects are more important in generic launch decisions in contrast to the estimates in Chapter 3 where global molecule sales were highly significant.

Finally, this section controls for the impact of the percentage retail sales for each molecule. This variable aims to control partially for the purchasing power of the demand side. Hospital purchases are usually determined by tendering with a high concentration among purchase groups. For example, hospitals and trusts in the UK

group together to negotiate price reductions with suppliers[108]. In addition, hospital prescriptions may be governed by formularies that restrict presentations of drugs to be selected within a therapeutic category in order to achieve bulk discounts. In general, prices in the hospital sector are lower compared to the retail sector because brand recognition is usually weak; single-providers are preferred for multi-source products, and cost is the main driver in contract tenders / bidding process[109].

Table D.24 in AppendixD.2, Section D.2.2.4 presents the robustness check with respect to percentage of molecule sales in the retail sector (this variable is defined quarterly as the percentage of retail sales in total sales of individual molecules for markets that have both retail and hospital sales in the database). A significant number of observations are lost because some countries have only retail channel data (Belgium, Greece, Spain, Sweden, South Africa and Turkey) or the combined sales for retail and hospital sectors (Sweden). For the US, retail sales are assumed to be composed of food stores, drugstores and mail sales. The overall evidence suggests that there is a positive relationship between share of retail sales and the hazard of first generic launch.

For parametric time duration specifications, the coefficient of percent retail sales is usually positive but not significant. On the other hand, for non-parametric estimates, the coefficient is statistically significant at the 0.05 level for *cloglog* and 0.01 for *logit*. These findings are in line with the findings of Magazzini (2004) who observes that the size of the hospital sector has a negative impact on generic market share in USA, UK, Germany, and France, in contrast to findings of Scott Morton (2000) which suggest a positive relationship between the share of hospital sales and the entry of generic products.

4.4.1.5 Firm Characteristics

The robustness of firm effects is tested by controlling for expected generic prices, expected market size, competition and molecule effects. Proxies that capture firm heterogeneity include:

- Log local sales of the corporation (USD$) quarterly (lnLocalCorpSales),

[108] The NHS Purchasing and Supply Agency (PASA) coordinates the tendering process. The supplier with a competitive tender (i.e. competitive prices) is selected to supply a given product at the specified price whenever it receives an order from one of the hospital trusts taking part in the tendering process

[109] http://www.publications.doh.gov.uk/generics/oxera_report_a6.htm

- Log global sales of the corporation (USD$) quarterly (ln_globalFirmSales),
- Global reach of the corporation, i.e. the number of geographical markets in which the firm has sales (CorpGlobalReach),
- Firm's molecule diversity which is measured as the number of molecules quarterly (FirmMolDivAtT_).

As in the case for molecule heterogeneity, firm effects show no robust significant effects across different specifications (see Appendix D.2, Section D.2.2.4, Table D.25 - Table D.28). Both for parametric and non-parametric specifications, local and global firm sales have a positive effect on the hazard of launch if calendar year dummies are excluded. When calendar year dummies are included firm sales have a negative coefficient. However, firm sales coefficients are not significant. Only the parametric specification with no calendar year dummies yields positive coefficient estimates for local firm sales.

The coefficient of firm's number of molecules is small but is robustly positive across different specifications, and significant for parametric specification with no calendar year dummies. Global reach of the corporation, i.e. the number of geographical markets in which the firm has sales, has positive coefficient estimate in 6 out of 8 different specifications; however, the effect is not significant.

These findings are in stark contrast to the findings regarding the firm effects in the launch of new molecules. For new molecules, speed of international launch depends significantly on firm size and economies of scope, whereas for generic launch international reach of the firm carries less importance (estimates are positive but not significant). Local firm sales seem to be better proxies compared to global firm sales in predicting the launch hazard for generic launch, which suggests generic launch strategies are more locally oriented compared to new molecules. This could be due to the fact that historically generic firms have been more locally oriented but generic companies are becoming increasingly global and growing through mergers to decrease their cost base. The significant importance of local firm sales may also indicate advantages in the tendering or price negotiation procedures with bulk purchasers such as hospitals.

A summary table for the main robustness checks and a comparison of the expected and estimated coefficient signs is presented in Table 4.7.

Table 4.7 Comparison of Expected and Estimated Signs of the Coefficients for the hazard of first generic launch

Factor	*Testable Hypotheses*	*Evidence from the Literature*	*Expected Sign of the Coefficient*	*Estimated Sign of the Coefficient*
Regulation	H1 a.1: High expected generic prices increase the hazard rate (decrease launch lag) for generic products	No direct empirical evidence	+ Price Coefficient (Higher generic prices, controlling for other factors, increase expected revenue and profitability for generic manufacturers)	+
	H1 a.2: Higher branded prices increase the hazard of launch of generic products	Evidence exists	+ Pb Coefficient (generic prices may be directly linked to branded prices; markets with higher prices tend to have higher generic prices)	+
	H1 a.3: Generic-branded price ratio Pg/Pb negatively affects hazard of launch.	No evidence on timing of generic entry	- Pg/Pb Coefficient (Keeping branded price fixed, lower generic prices allow generics to capture a higher volume share)	-
Market Size	H1 b.1: The higher the branded molecule sales prior to generic launch (in $ or SU), the higher the hazard of launch	Empirical evidence exists for $ sales of branded products	+ Market Size Coefficient (Both the sign of SU and USD sales are expected to be positive)	+
	H1 b.2: The higher the expected generic market size (= branded molecule sales * the average generic share in the local market), the higher the hazard of launch	No direct empirical evidence	+ Expected Market Size Coefficient (Market size increases incentives for entry as the net present value of entry is increased)	+
Competition & Market Structure	H1 c.1: A higher number of expected generic competitors decreases the hazard of entry	No evidence	- Coefficient for number of competitor firms (Theoretically I have shown that number of generic entrants has a negative impact on expected profits)	- (concave relationship); effect not robustly significant

	H1 c.2: The higher the number of substitute molecules in the therapeutic class, the lower is the hazard rate	No evidence	- Coefficient for Substitute Molecules (Either reference pricing or competition will drive prices and potential profits down)	+ ; effect not significant
	H1 c.3: The higher the Herfindahl concentration index of generic manufacturers at the therapeutic class level, the lower the hazard rate	No evidence	- Concentration Coefficient (in Chapter 3 concentration in on-patent sector had a negative coefficient estimate. Industrial organization literature predicts that concentration reduces the equilibrium level of entry)	+
Molecule	H1d.1: Generic entry for therapeutically/commercially important molecules is faster (higher branded prices and higher profit potentials)	No evidence	+ Coefficient for Molecule's Global Reach	- but not significant
			+ Coefficient for Molecule's Global Sales	No robust evidence
	H1d.2: The longer the lag for the entry of the originator molecule, the faster the generic entry	No evidence	+ Coefficient for the Lag of the Originator (longer lags imply shorter exclusivity and lower brand loyalty)	+ across models; not significant
	H1 d.3: Percentage of molecule sales in the retail sector increases hazard of launch	Contradictory	? (prices in the hospital sector tend to lower than in the retail sector but volume effect could dominate)	+; significant for non-parametric models
Firm	H1 e.1: Firm economies of scope (number of molecules in the portfolio) increase the hazard of launch	Evidence exists	+ Economies of Scope Coefficient (Economies of scope allow lower-cost entry as the firm can switch quickly and less costly from one product line to another. Also, knowledge spillovers across different product lines may further lower development and entry costs)	+ and significant
	H1 e.2: Firms' scale has positive effect on the hazard of launch.	Evidence from	+ Coefficient for Firm's Global/Local Sales (Scale effects are expected to be less	+ for local; no robust evidence for

		the branded sector; No firm empirical evidence exists for the generic sector	important than in on-patent sector due to lower R&D and advertising costs. But scale economies may allow vertical integration in the supply chain and mergers with other firms to decrease costs)	global sales
			+ Coefficient for Firm's Global Reach A wider global reach indicates potentially bigger firm size and higher familiarity with diverse regulatory environments	+ but not significant

4.5 CONCLUSION

This chapter aimed to investigate how regulation affects the relative adoption speed of first generic products across the main OECD markets during 1999-2008 controlling for expected market size, competition, molecule and firm characteristics. Consistent with hypothesis H1 a.1 (High expected generic prices increase the hazard of generic adoption), expected generic prices increase the hazard of first generic launch across OECD markets, with higher priced markets adopting generic products quicker. This is consistent with the trade off between static efficiency and dynamic efficiency, or cost cutting competition and innovation. Controlling for branded prices, a higher price differential between generic and branded prices increases hazard of launch, which is consistent with hypotheses H1 a.3 (Generic-branded price ratio Pg/Pb negatively affects hazard of launch.). Second, consistent with hypotheses H1 b.1 (The higher the branded molecule sales prior to generic launch (in $ or SU), the higher the hazard of launch) and H1 b.2 (The higher the expected generic market size, the higher the hazard of launch), empirical findings suggest that expected generic market size (in USD$) is a significant determinant of launch, controlling for price, competition, firm and molecule characteristics.

Competition plays a significant role in the adoption of first generic products. The higher the concentration of generic manufacturers in the ATC4 in each country, the higher is the hazard of launch, which contradicts hypothesis H1 c.3 (The higher the Herfindahl concentration index of generic manufacturers at the therapeutic class level, the lower the hazard rate). This implies that if the generic sector is highly fragmented at the therapeutic level, then incentives for entry are reduced. This is in contrast to the findings for new molecules, where competition at the therapeutic level was found to increase the entry of patent-protected new molecules (see Chapter 3). Generics are commodity products with little room for differentiation and compete solely on price. Consistent with hypothesis H1 c.1 (A higher number of expected generic competitors decreases the hazard of entry), a fragmented generic market with a higher (potential) number of generic manufacturers depresses generic prices, profitability and incentives for launch. On the other hand, molecules in the branded sector compete based on quality, product-differentiation and brand loyalty built through advertising. New

molecules in a given therapeutic category are usually improved versions of older molecules, with fewer side effects, and hence, can capture market share from already existing molecules.

Another difference in determinants of first launch for branded and generic products is the impact of the number of molecules in the therapeutic category. Number of molecules for the branded sector increases the hazard of launch for branded products significantly (see Chapter 3, Section 3.4.1.2). However, the number of substitute molecules in the ATC4 therapeutic group is not statistically significant in generic launch timing decisions after controlling for expected generic price and market size, which neither confirms nor refutes hypothesis H1 c.2 (The higher the number of substitute molecules in the therapeutic class, the lower is the hazard rate). This result can be explained by the fact that existing molecules are not exact substitutes for the launching generic. Substitute molecules in the therapeutic subgroup, however, can affect generic viability directly if reference groups are defined at the therapeutic sublevel. Regulators tend to favour groups defined by active ingredients and chemically related active substances that are pharmacologically equivalent; the concern being that therapeutic referencing may lead to the prescription of less effective medicines within the therapeutic group if this allows the patient to avoid co-payments (Simoens and de Coster 2006).

Overall, logit and cloglog parameter estimates are very close. Also, AIC and BIC are very close for cloglog and logit specifications; the logit specification is marginally better based on the AIC and BIC but the difference is not significant. In general, parametric specification results have significantly lower AIC and BIC compared to the non-parametric specification both in cloglog and logit specifications. This might be due to the fact that the parametric specification is much more parsimonious compared to the non-parameteric specification that can include up to 117 dummies for monthly intervals. Also severe multicollinearity was observed for the number of generic firms in the country (proxy for competition) and calendar year dummies. However, multicollinearity was resolved by using the concentration index for generic firms at the therapeutic subgroup level.

The most unexpected finding in this chapter is that molecule or firm characteristics do not have a robust effect across different specifications. Consistent with hypothesis H1 e.2 that firm scale has positive effect on the hazard of launch, local firm sales are more significant in predicting hazard of launch compared to global firm sales, controlling for expected generic price, market size and competition. Competitive advantage in the generic business is based on either a low-cost base or differentiation in forms that are difficult to manufacture and market (Gorka 2009). Global players would normally be expected to have a higher ability in overcoming the barriers to entry and launching quicker on average; however, the empirical evidence indicates that local presence of the firm is more significant in timing of generic launch decisions. This result, however, may change in the near future as the generic firms become more globalized and grow through mergers and acquisitions. In addition, firms' portfolio diversity (number of molecules) suggests that there are economies of scope which can be shared across different molecules. Consistent with hypothesis H1 e.1 that firm economies of scope increase the hazard of launch, firms with a higher number of molecules on average have quicker generic launch.

The most significant findings regarding heterogeneity in molecules are the impacts of the originator product launch delays and percentage of molecule sales in the retail sector versus the hospital sector. Consistent with hypothesis H1 d.2 (the longer the lag for the entry of the originator molecule, the faster the generic entry), the delay of the originator product relative to the global launch date of the molecule increases the relative delay in the timing of generic availability in models with calendar year dummies.

In markets where data is broken down by hospital versus retail sales, the hazard of first generic launch increases with higher percentage retail sales. This is potentially explained by the fact that prices in the hospital sector are lower compared to the retail sector due to predominant use of tendering contracts for the purchase of medicinal products. Hospitals prefer single-providers for multi-source products, and cost is the main driver in the bidding process. By restricting presentations of drugs to be selected within a therapeutic category hospitals may negotiate substantial price reductions off the list price of medicines. Given the increasing use of tendering procedures in ambulatory care (Dylst and Simoens

2010), this finding suggests that incentives for generic entry and extent of generic competition might be further reduced.

Generic entry has profound implications on the competitive landscape and the average price levels of the originator as well as the sales volume of the originator. Moreover, generics affect prices of other molecules within the same therapeutic category through competition or reference pricing systems. Generics increase access to drugs by the reduction in branded product prices. According to Simoens and de Coster (2006) increased generic substitution in 2004 would be expected to reduce public expenditure on originator medicines by at least 20% in the main European countries (Simoens and de Coster 2006). DG Competition estimates that average prices dropped by 20% after the first year and 25% after 2 years, and that immediate generic entry following patent expiration would offer 20% savings on expenditures[110].

Given the potential savings offered by generics to public health systems, improving access to generics and reducing delays for existing treatments is highly important from a public health policy perspective. Many pharmaceutical markets such as France, Spain, Italy and Japan all have very low volume penetration rates in the off-patent sector, less than 20% vs. over 70% in the US, which suggests there is a great potential for generic growth in these markets (European Generic Medicines Association 2007b; Gorka 2009). Empirical evidence in this chapter demonstrated that the impact of expected generic prices and market size on timing of generic entry decisions is statistically significant. Furthermore, demand-side measures such as generic substitution aimed at promoting generic utilization is effective in reducing international differentials in the adoption of first generics.

Limitations

The main limitation in this study is that the hazard of generic availability is estimated with respect to the first generic availability in the global market. Ideally, the delay should be defined relative to the country-dependent patent expiry or SPC protection expiry dates. Availability of patent expiry dates would enable to characterize the monopoly period during which the originator develops brand loyalty. However, the relative delay of the originator molecule in each

[110] http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/fact_sheet_1.pdf

market is used as a control to account for the reduced exclusivity period in each market.

In addition, the study is not able to quantify the delays due to price approval procedures within price-controlled markets. Following market authorization in the majority of European markets generic products face additional delays due to pricing and reimbursement approval except for free-priced markets such as UK, US, Germany, and Netherlands. Although the Transparency Directive 89/105/EEC has set a 90-day limit for both pricing and reimbursement decisions, in practice delays have been shown to exceed these limits substantially (European Generic Medicines Association 2007a; Simoens 2008). Due to unavailability of protection expiry dates and pricing and reimbursement approval dates these delays could not be quantified in this study.

This study does not account for potential cases where the first generic is an authorized generic, i.e. a generic medicine marketed by the originator company (either directly or via a license to a generic manufacturer) but sold under a generic name for a lower price. Authorized generics may reduce the incentives to entry for other generic manufacturers by entering before or at the time of patent expiry (Peny and Covilard 2007). Authorized generics have been suggested as a potentially significant cause of delay both in the US and most recently in Europe by the DG competition (2009). In the US, authorized generics may dissipate the first mover advantage that grants 180-day market exclusivity provisions to the first generic entrant[111],[112]. Finally, this study does not account for the heterogeneity in Europe's local legislations regarding the current patent and registration systems. Patent validity and infringement issues are governed by national laws and handled by different rules in each country, which increases financial costs as well as time burden on the generic manufacturers within Europe.

[111] In 2003, the Gregg-Shumer Act included forfeiture provisions that result in the generics company losing its exclusivity if the generic company is found to have made an agreement with the originator not to launch or to take product from the originator.

[112] A recent US legislation (Protecting Consumer Access to Generic Drugs Act of 2009) has been proposed to ban anticompetitive settlements of patent infringement litigations. Most commonly such agreements involve payments (also known as reverse payments) made by branded manufacturers to generic companies in return for a commitment to delay the entry of generics extend the market exclusivity for high-priced brands and defer legitimate competition from generics

Future Research

Additional data on the expiry dates of exclusivity protection, pricing and reimbursement approval and whether the first generic is an authorized generic would allow quantifying the magnitude of delays due to pricing or reimbursement in individual markets. From a policy perspective promotion of both timely entry and rapid take-up are important. This study considers time to the first generic entry only. A natural extension would be to consider the extent of entry and generic diffusion across different markets conditional on the number of existing competitors. Usually, the first generic entrant has asymmetric costs with respect to the following entrants because of the patent litigation cases that have to be overcome. This suggests differential barriers to entry with respect to first and later generic entrants. Also, first entrant mainly competes against the originator whereas price competition intensifies as more and more follow-on manufacturers enter the market. There are only few studies that model the intensity of generic entry and uptake in markets outside North America.

Finally, this chapter has focused on investigating mainly the impact of supply-side measures through expected generic prices and reference price system dummies. On the demand-side only the availability of generic substitution option to the pharmacist has been included as a dummy variable. The analysis could be further extended to assess the impact of other demand-side measures such as physician incentives and patient co-payments. Co-payments are important as they determine patients' price sensitivity and the demand for generic medicines in the context of a reference pricing system. Although in most European countries the patient's contribution to the cost of pharmaceuticals is limited, it would be interesting to investigate how risk-sharing through co-payments affect incentives to generic entry and timing of generic availability.

An area which is gaining importance and attention is the upcoming patent expiries of biopharmaceutical patents; patents of most current biologics are expected to expire during 2010-2024[113]. Biosimilars, generic versions of molecules produced by biotechnological means, are expected to offer new opportunities for the growth

[113] Regulatory developments facilitating follow-on biologics (biosimilars) are already on the way. Europe adopted a legislative framework for biosimilars in 2004 and the US has introduced new bills on biosimilars to the US Congress in 2009.

of the generic industry. Biologics constitute some of the most-expensive medicines and are therefore major targets for potential cost containment[114]. The analytical framework in this chapter can be extended to analyze the entry of biosimilar products to inform policy makers about the nature of the hazard of launch of follow-on biologics.

Contribution

The main contribution of this chapter is that timing of first generic entry has been analyzed for the first time using a multi-country perspective controlling for expected generic prices and market size, competitive environment, firm and molecule heterogeneity. IMS price and volume data used in this analysis is one of the most reliable data source both in the industry and academic research. The analysis period comprises the last two decades (1999-2008) and therefore has immediate policy implications. The panel data structure exploits variation both over time and over country-molecule pairs in regressions. Although I have aimed to minimize issues of endogeneity by using lagged or moving average prices, the analysis could be extended to endogenize price and entry.

[114] According to the Federal Trade Commission, Remitade used to treat rheumatoid arthritis costs $20,000; Avastin used to treat lung cancer costs $100,000 and Cerezyme used to treat Gaucher disease costs $300,000 per patient-year (Jorge 2010)

CHAPTER 5

5 CONCLUSION

5.1 Introduction

New technologies contribute to economic growth because of their superior competitive advantage generating more efficient production processes. Healthcare technology and technological innovation play a key role in the delivery of health services and are main drivers of optimal health outcomes (OECD 2005b). Health technologies include pharmaceuticals, medical devices, diagnostic agents, surgical procedures and organizational systems that provide health care. Policy-makers face the need to develop policy instruments that promote timely adoption and optimum level of technology diffusion ensuring that new technologies adopted are cost-effective and consumers have an equitable access to these technologies. This thesis has explored the cross-country adoption of pharmaceutical technologies in the health care sector within the OECD during 1999-2008 focusing on the impact of price regulations.

The thesis adopted a cross-country perspective because most theories and empirical evidence on technology adoption and diffusion so far have been in a single geographical market setting (Stoneman 2002). According to Stoneman (2002), there are "no modelling frameworks to reflect or even stand up against the models provided for analysing diffusion within firms, industries or economies". The lack of theory and empirical evidence on the international adoption and diffusion of technology to inform policy-making on how and why technologies spread from country to country and lack of empirical evidence on the impact of regulation on cross-country technology adoption formed the main motivation for the research carried out in this thesis. The thesis offers a major empirical contribution to our understanding of drivers of pharmaceutical technology adoption in the healthcare sector.

Pharmaceutical technologies considered in the thesis include: i) new innovative molecules that offer improved benefits over existing alternative treatments or address unmet medical needs; and ii) generic imitative technologies that offer the same therapeutic benefits as the originator products at lower prices. The static-dyanmic efficiency trade-off has been a key challenge for pharmaceutical policy makers. The sustainability of the pharmaceutical sector depends on balanced interplay between on-

patent products that improve health outcomes but are usually cost-increasing technologies and cost-saving off-patent technologies that create incentives for future innovations through fierce price competition. The adoption of these complementary technologies was analyzed using the first launch date of products with the same active ingredient as the adoption date of the technology. The scope was limited to adoption only and diffusion, i.e. the differential intensity of new pharmaceutical molecule or generic drug use in individual markets, was not analyzed. The thesis offers a significant contribution to the literature by empirically analyzing the impact of expected prices, the main proxy of price regulation, on the probability of launch for potentially global new molecules and first generic competition controlling for market structure, competition, and firm and molecule heterogeneity.

Launch delays in the adoption of new breakthrough or cost-effective technologies have significant equity, efficiency, and health outcomes implications. Development of new drugs has been proposed as a more cost-effective way of improving population health and increasing life expectancy (Lichtenberg 2004; Grootendorst, Piérard et al. 2009). Delays in launch or non-launch of new medicines, therefore, have clear negative implications both on dynamic efficiency and public health outcomes. On the one hand, new drug products are granted market power through patents to allow appropriability of R&D investments and ensure the sustainability of future innovations. On the other hand, above marginal cost pricing results in allocative inefficiencies (Motta 2004). Policy makers are under increasing pressure to contain rising pharmaceutical expenditures and reduce budget deficits. In the majority of the OECD markets, price controls are in place to correct market failures by putting limits on new medicine prices or on the amount reimbursed by public payers. Together with significant generic promotion strategies undertaken across the OECD to create low-price competition post-patent expiry, pricing pressures have increased for generics as well (Schulz 2004).

The trade-off between static and dynamic efficiency has become even more severe with the rising drug development and market access costs coupled with the advent of the economic and financial crisis in the past few years. The picture gets even more complicated when the second dimension of social welfare, equity in access to health improving technologies, is considered. Policy makers in all OECD countries show concern for distributional justice, i.e. equity of access to health care, albeit with varying degrees in individual markets. Equity in health has widely been defined as the absence of systematic disparities in health (or in the major social determinants of health)

between groups with different levels of underlying social advantage/disadvantage[115]. Equity in health is also closely related to the right to health stated in the WHO Constitution and international human rights treaties (Braveman and Gruskin 2003).

Differences in the likelihood of receiving appropriate treatment for a disease within a given country or across different markets causes concern from an equity perspective. Delayed adoption of new breakthrough drugs could lead to compromises in heath outcomes and disparities in health compared to populations that have significantly faster access to these technologies. Timely adoption of cost-effective technologies such as generic pharmaceuticals increases the affordability of drugs. Given that equity of access to healthcare implies access to healthcare based on need rather than ability to pay, prompt generic adoption will improve the access to pharmaceutical technologies for the socially less well-off individuals in the society.

How adoption of new technologies changes with respect to different regulatory schemes has been a question open to empirical scrutiny in many sectors. This question, however, is highly relevant for the pharmaceutical sector as it is one of the most heavily regulated industries and one that thrives on innovation and sustainability of R&D investments. The complexity of regulatory systems and changing dynamics in prices and across therapeutic groups in individual countries makes a normative analysis extremely challenging. Therefore, positive empirical evidence carries an important role in informing policy making. There is a lack of empirical evidence in the literature that uses product specific price and volume information to control for the net effect of regulation on the hazard of launch, mainly due to the diffuculty in obtaining such data. The paucity of the evidence in the off-patent sector, in particular, is striking and has recently received increasing attention from the competition authorities in the US and EU as the importance of this sector continues to increase with the expected expiries in the near future, including the expiries of biotechnology products that tend to be highly priced.

This chapter will summarize the conclusions and findings from each chapter in Section 5.2; highlight the contributions to the literature in Section 5.3; discuss policy implications in Section 5.4; acknowledge limitations and suggest future research areas in Section 5.5.

[115] Discussion on the main theories of equity can be found in Pereira (1993); Olsen (1997); Sassi, Archard et al. (2001).

5.2 Conclusions from Each Chapter

Chapter 1 introduced the motivation of the thesis and the research hypotheses to be tested in individual empirical chapters. Chapter 1 also provided an overview of economics of regulation in the pharmaceutical industry and outlined the main types of pricing and reimbursement schemes in the US-EU5.

Chapter 2 explored the nature of drug delays for new molecules and generics both across the main OECD markets and over time from 1960 to 2008 to set the motivation for the following empirical chapters. The analysis period was broken down into three sub-periods (1960-1984; 1984-1995; 1995-2008), with the cut-off dates defined by the US Hatch-Waxman Act in 1984 and the establishment of the European Medicines Agency in 1995. IMS local and global launch dates were used to estimate mean (and median) survival times for each market during these three periods by non-parametric survival analysis (Kaplan-Meier estimates). In addition, the impact of these regulatory changes was assessed by random and fixed effects Cox proportional hazard model and difference-in-differences analysis.

Chapter 2 found that stringent market authorization requirements for new pharmaceutical products in the US after 1962 resulted in a significant US drug lag in the introduction of pharmaceutical innovation vis-à-vis Europe during 1960-1984. However, financial incentives of the 1984 Hatch-Waxman Act proved effective in closing this lag. Over decades, a considerable increase in speed of market access is observed following the global launch of molecules. This evidence was robustly consistent with the view that adoption of pharmaceutical products is responsive to changes in the regulatory environment.

Reduction in legal transaction costs due to harmonization in marketing authorization requirements has been effective in reducing relative delays across countries. In addition, a more streamlined central approval procedure by EMEA has reduced differentials in new pharmaceutical technology adoption in a fragmented European market enabling more even access to new molecules. However, a pattern of delay still exists due to country-specific differences in pricing and reimbursement regulations following marketing authorization. The evidence suggested that new molecule launch strategically takes place first in higher-priced EU markets because of threat of arbitrage and price dependency across the member states. Finally, Chapter 2 concluded that markets with

more aggressive pricing controls face temporal disadvantage in access to cost-saving generic products relative to the market of first generic launch.

Chapter 3 investigated the impact of various factors on cross-national roll-out speed for new pharmaceutical innovations that address existing unmet medical needs through the introduction of either first-in-class molecules or molecules with an improved quality profile over existing alternatives in the market. Chapter 3 used semi-parametric and parametric discrete-time survival analysis methods to incorporate the impact of regulatory (structural) and strategic barriers to market entry (regulation, market, firm and molecule characteristics) on the time to local launch. IMS data on local launch dates of new molecules were used to define the survival period for molecule-country pairs relative to the first global launch date. Lagged competitor prices in the same therapeutic subgroup were chosen as the main proxy for regulation. Cox regressions and discrete time survival analysis using complementary log log regressions were carried out for molecules that have launched globally (in at least 10 markets) to avoid bias resulting from locally-oriented molecules and increase the generalizability of the results, which has been the main criticism directed at previous studies in the literature.

Chapter 3 found that expected prices and market size significantly increases the hazard of launch of global molecules. Pharmaceutical corporations optimize launch sequences globally to optimize profits by delaying the launch of innovative molecules in markets with lower prices and/or lower market size. Higher molecule concentration at the therapeutic subgroup discourages fast adoption as the industrial organization literature predicts. This fortifies the impact of low prices on competition. Lower potential profits result in fewer entrants, which in turn results in higher concentration at the therapeutic subgroup, further decreasing the incentives for entry. Among factors that shape the external firm environment, expected prices emerged as the most significant factor. This is expected for new molecules because prices not only affect local profit potentials but also have knock-on effects in foreign markets through external referencing and parallel trade.

Chapter 3 found significant firm and molecule effects on the probability of launch in markets following first global launch. Firms with a more established local presence have advantages in timing of launch, which could be due to negotiation power in the pricing and reimbursement approval. Similarly, firms with a wider global reach and firms of a larger size (higher global sales and number of molecules) access markets

faster compared to smaller firms. This suggests significant advantages due to economies of scale and scope in distributing R&D costs and knowledge across more markets and product pipelines to overcome fixed costs of entry. Similarly, therapeutically more important molecules, of wider global diffusion, have higher hazard rates and diffuse across international markets faster.

Chapter 4 focused on differentials in adoption of first generics, imitative competition that offer healthcare providers and payers an effective tool for containing pharmaceutical expenditures without jeopardizing health outcomes. The main research question addressed was how pricing and reimbursement regulations affect timing of first generic launch across the major OECD markets during 1999-2008. The motivation for this chapter stems from the increasing focus on genericization as a cost-effective tool to cut expenses for bioequivalent treatments that are more expensive while freeing up resources for payers to afford more innovative treatments directed at unmet medical needs. Chapter 4 estimated the impacts of various cofactors (regulation, market, firm and molecule characteristics) on the hazard of the first generic launch for each molecule-country pair following the first generic global adoption.

Regulation is mainly captured by lagged expected generic prices defined as the product of lagged average retail branded prices and the median generic-branded price ratio in the destination market. This approach offers a more refined approximation compared to controlling regulation exclusively by treatment dummies for regulation. Based on the outcomes in Chapter 3 and the grouped nature of survival times in the IMS database, the survival analysis was carried out with discrete time implementation of the proportional hazard model using complementary log log regression. Proportional odds model using logistic regressions were carried out for robustness checks and to control for potential violations of the proportional hazard assumption. Parametric and non-parametric duration dependence specifications were estimated both for cloglog and logistic regressions to capture patterns in coefficient estimates. Estimates were obtained for generic molecules that launched first after the establishment of a single European market in 1993 and that launched both in the US and UK to exclude generics launched exclusively in one market.

The most significant and robust finding of Chapter 4 is the highly significant positive effect of expected generic prices and expected market size on the hazard of first generic launch. Controlling for branded prices, a wider difference in branded and generic prices

favours quicker launch as this offers generics to capture a higher market share. Increase in expected market size by one standard unit for generics was associated with a higher increase in the hazard of launch compared to an increase of one-standard unit in expected prices, which confirms the importance of capturing a significant volume for the viability of the generic market. Extent of potential generic competition was found to inhibit quick entry of generics. Intra-molecular competition in the therapeutic subgroup did not have a significant effect on the hazard of generic launch. Firm-level controls exhibited more locally oriented strategies for generics compared to new molecules in Chpater 3 where firm's global sales were substantially significant.

5.3 Contributions of the Thesis to Literature

Economic theory predicts that structural and strategic barriers to entry reduce the extent of entry. One of the main structural barriers in the pharmaceutical industry different from more traditional manufacturing sectors is regulation. To date, there is relatively scanty evidence regarding the impact of regulation on the adoption of innovative pharmaceutical technologies; the evidence is even scarcer on the timing of generic adoption. This thesis has focused on the impact of regulation as a structural barrier to entry in the on-patent and off-patent pharmaceutical markets in the main OECD markets. In addition, as Stoneman (2002) has highlighted, the economics literature suffers from a severe lack of theoretical framework and empirical evidence on the international adoption and diffusion of technology. The research in this thesis has also addressed this gap by analyzing determinants of pharmaceutical technology adoption in a cross-country setting.

Although the thesis has provided evidence on the impact of pharmaceutical regulation on time-to-market launch, the optimal form of pharmaceutical regulation and the degree of price mark-up consitent with dynamic efficiency were not addressed. The results, however, shed some light on potential implications of price controls on efficiency and equity. Consistent with economic theory, price regulation pushes prices down towards marginal costs and brings short-term efficiency gains through lower prices both for pharmaceutical innovation and generic competition. However, the delays in adoption due to price controls and price linkages across interdependent markets results in temporal inequity in access to health improving and cost-saving pharmaceutical technologies. Therefore, the short-term efficiency gains brought about through price

regulation should be weighed against potential long-term implications on public health outcomes and dynamic efficiency.

Additional contributions of the thesis, which are summarized below, comprise the quality of the data used, the robustness of the methodology adopted and the scope which includes the first time comparison of differential delays in adoption of generics across the OECD markets.

5.3.1 Data

The thesis uses a comprehensive IMS Health dataset on drug prices, sales volume, launch dates and launching corporations during 1999-2008 in the OECD. This is the most up-to-date and reliable data in the literature. The data includes all of the therapeutic subgroups with positive sales during 1999-2008 in 20 countries. Such data is extremely difficult and costly to access. Therefore, previous studies have broadly relied on treatment dummies to control for price regulation.

Treatment dummies cannot capture the nuances in individual therapeutic subgroups and the variations in prices and sales volume over time, which are the main drivers of pharmaceutical corporations' launch strategies. Using IMS data, I was able to define expected launch prices and expected market sizes for launching products, which is a more sensitive and correct proxy for the impact of price controls and heterogeneity in the market environment.

The data covers the major countries of interest in the global pharmaceutical market, which account for more than 80% of global pharmaceutical sales. Also, these countries include markets where the major proportion of global R&D takes place. The molecules analyzed were restricted to potentially global molecules. The policy implications of price controls in these markets, therefore, are substantial for the global industry.

5.3.2 Methods

Discrete Survival Analysis

The most sophisticated methodological approach in the literature that has been adopted so far is discrete time survival analysis using complentary log log analysis (Danzon and Epstein 2008). In the last two empirical chapters, the thesis has adopted this methodology to account for the interval-censoring in failure (launch or adoption) times

as well as right censoring for molecule-country pairs that did not launch until the end of Q3 2008. However, overall I have used more extesive control variables to avoid omitted variable bias. In addition, the thesis investigated the robustness of the cloglog model by comparing it to other common methodologies such as Cox and logit regressions. In Chapter 3, I compared estimates from a continuous Cox proportional hazard model with estimates from a discrete time proportional hazard model with cloglog regression. Overall, I concluded that discrete-time specification fits the data better, which I expected a priori given the interval-censored nature of the launch dates. In Chapter 4, I compared estimates from proportional hazards model with complementary log log link (cloglog regression) with estimates from proportional odds model with a logit link (logit regressions). Parameter estimates and marginal effects turned out comparable across these two different regression models, which highlights the fact that the hazard of adoption is relatively small. Overall, Akaike and Bayesian Information Criteria (AIC and BIC) were comparable across the logit and cloglog estimates. The logit model, however, had slightly lower AIC and BIC in some of the robustness checks.

Identification of Regulation and Competition

The main limitation in previous studies has been heavy reliance on treatment dummies to control for the effect of regulation. The thesis relied on lagged ex-manufacturer prices as a more sensitive control for the net impact of regulation. In the on-patent sector, expected prices were defined using average prices of molecules in the same therapeutic subgroup (ATC4) and in the off-patent sector the expected price was defined as the average price of the originator molecule times the median generic-branded ratio in the market. Similarly, expected market size was estimated by lagged sales (in $ and SU) in the therapeutic subgroup ATC4 for new molecules, and for the generic entry analysis by lagged branded sales prior to generic entry times average generic share in the local market.

Different from prior studies in the literature, the impact of competition was investigated using the Herfindahl Hirschman concentration index for molecule sales in the same ATC4 in Chapter 3 and the sales of generic firms in ATC4 in Chapter 4. This measure of competition accounts for unequal market shares. A crude number of competitors as a proxy of competition gives equal weight to each individual firm and molecule, and thus, may not be able to capture the importance of market share that these firms or molecules account for.

Control for Market Structure, Product and Firm Heterogeneity

Disentangling the effects of market structure, firm and molecule characteristics on the probability of launch enabled estimation of price and market size coefficients more precisely. Both Chapter 3 and Chapter 4 exploited the variation over time and molecule-country pairs due to the panel nature of the data. The errors were clustered at the molecule-country level (i.e. objects under risk in the survival analysis) to account for potential autocorrelation over time.

Extensive Robustness Checks

The second major contribution is that the thesis carried out extensive robustness checks to identify how sensitive parameter estimates are to the regression methodology and duration specification. Results were compared across cox and cloglog estimates in Chapter 3; cloglog and logistic estimates in Chapter 4. Duration-specification in discrete-time survival models was estimated: 1) parametrically by assuming a quadratic in time since risk onset, and 2) non-parametrically by including dummies for each monthly interval obviating the need for prior assumptions about the time dependence of the baseline hazard. In addition, in Chapter 4, I investigated the sensitivity in parameter estimates with respect to the inclusion/exclusion of calendar year dummies that were multicollinear with the market structure variable, number of generic firms over time.

5.3.3 Content

First Analysis of Evolutionary Trends

The thesis provided the first comparison of launch lag trends across markets and different periods during 1960-2008. This analysis clearly indicated that pharmaceutical corporations launch strategies are highly responsive to changes in the regulatory landscape and the legal transaction costs of entry. I have tested for the impact of the two main regulatory changes using a quasi-experiment framework with difference-in-differences analysis as well as fixed and random effects Cox proportional hazards model.

Evidence on Adoption of Innovative and Generic Competition

The sustainability of pharmaceutical innovations and generic competition is a key policy goal to maintain the balance in static efficiency and dynamic efficiency. The thesis, therefore, provided a more holistic approach by analyzing the impact of price

controls both on the adoption of innovation (new molecules) and imitative competition (generics).

The analysis for adoption of new molecules extended the work of Danzon and Epstein (2008) by using molecules that launched in at least 10 markets. Methodologically, I also employed extensive controls for firm, molecule and therapeutic subgroup competition effects to isolate the effects of these variables, potentially reducing the variability in the parameter estimates.

The literature had a significant evidence gap regarding the impact of price controls on timing of generic entry. The thesis analyzed for the first time the impact of differing pricing controls on the adoption of first generics across main OECD markets using discrete-time survival analysis. In addition, I used proxies that are more refined for expected generic prices and market size by controlling for branded-generic price ratios and average generic shares captured in individual markets.

5.4 Policy Implications

Different cost containment policies directed at the supply and demand side in order to contain costs and increase efficiency have clear and significant implications on the adoption of pharmaceutical innovations and commoditized generic copies. These policies may distort the process whereby new medicinal products and first generics are adopted and should be weighed against the potential implications of late access to medicinal products in the on-patent and off-patent sectors. Generics introduce competition and increase incentives for innovation. On the other hand, growth in the generic sector thrives on the expiry of new molecules; reduced incentives to entry for innovative molecules will eventually hamper the sustainability of the generic sector. Policy makers should consider long-term implications of hampered market entry and distortions in the incentives for innovation.

Empirical results provided significant evidence that product launch strategically takes place first in higher-priced EU markets as a result of threat of arbitrage and price dependency due to external reference pricing. This positions European markets with low prices and/or small market sizes such as Portugal at a significant disadvantage. Price regulations may impose welfare losses through slower adoptions of new medicines, particularly in cases when the innovations that are delayed are cost-effective from a societal perspective. Empirical evidence shows that lack of access to new drugs leads to

compromises in health outcomes (Schoffski 2002), shifts volume to older molecules of lower therapeutic value (Danzon and Ketcham 2004) and results in higher expenditures on other forms of medical care and compromises in quality of health care (Kessler 2004; Wertheimer and Santella 2004). Innovative medications offer economic benefits through fewer work days missed and lives saved (Lichtenberg 1996; Lichtenberg 2003a; Hassett 2004; Lichtenberg 2005). Therefore, savings to be accrued from lower prices in the short-run should be weighed against long-term implications of reduced and delayed access to innovation on public health outcomes and implications on the innovative activity in the pharmaceutical sector.

Significant advantages to economies of scale and scope in the on-patent sector emerged from the analysis in this thesis. Given the incentives for mergers and acquisitions, this may sequentially result in higher concentrations, higher barriers to entry and reduced competition. There is strong evidence that innovation diffuses quicker to more competitive therapeutic subgroups. Policy makers should actively promote competition in the branded sector by reducing barriers to entry due to transaction costs in pricing and reimbursement approval.

R&D activity of leading pharmaceutical companies is largely carried out in the major OECD markets included in the analysis; in addition, the sales generated in these markets accounts for a significant proportion of global profits. Findings regarding the impact of regulation on timing of launch and negative profit implications have global implications. Low prices have already been shown to discourage R&D and future innovation (Giaccotto, Santerre et al. 2005; Vernon 2005). Reducing delays for pricing and reimbursement by setting more transparent and objective criteria will allow higher returns to R&D for companies stimulating further innovation and allow more timely patient access to new medicines, as well as timely access for cheaper alternatives both for the patients and payers. From a cross-country perspective, reducing the differential delays for globally important molecules will enable a more equitable access to new and possibly more effective treatment alternatives.

The growing importance of pharmacoeconomic assessments (known as "the fourth hurdle") and the drive for value-for-money has been a growing concern for pharmaceutical corporations in Europe, the US and increasingly in emerging pharmaceutical economies. Pharmaco-economic assessments are promising the efficient use of resources and the promotion of the right type of R&D investments. The

likelihood of getting cost-effectiveness approval or approval for restricted indications significantly affects price negotiations and the potential market of new medicines, and therefore, may have implications in market entry decisions. Chapter 3 demonstrated that free-priced markets have faster new pharmaceutical adoption. However, these markets are also the ones who have the most stringent criteria for reimbursement through heath technology assessments. Although these evaluations do not have direct impact on time to market, they have an indirect impact on allowable price and potential profit. The complexity of launch and market decisions is further increasing due to risk sharing and early access schemes. The implications on differentials in market access remain to be seen and can be explored as further research.

Chapter 4 provided evidence that a fragmented pricing and reimbursement environment across Europe causes delays in the market entry of first generic medicines. The evidence shows that price regulation may delay the timing of entry for the first generic if expected generic prices are lowered and/or the generic-branded price differential is kept small as a result of policies such as reference pricing. Generics tend to be more expensive in countries that adopt a free market approach and in countries that have a mature generic medicine market (Simoens 2007)[116]. In markets that have stringent price regulations prices of originator molecules are driven down throughout the product lifecycle, which discourages market entry of generic medicines. The originator price in free markets, on the other hand, may increase following patent expiry. Limited diffusion of generics in markets with strict price controls restricts competition post-patent expiry (Adriaen, De Witte et al. 2007). In addition, competition between generics is important to reduce prices in excess of price reductions imposed by price controls and increase the price difference between the originator and generics.

Price linkages between generic and originator medicines in some member states may hamper achieving a competitive generic-branded price ratio. Generic prices in the US and the EU will be subject to further downward pressure on prices as generics are increasingly manufactured in Asian countries such as India, which will have further implications on the importance of capturing high volume share for generics.

[116] Also penetration of generic medicines is more successful in countries that permit relatively free pricing of medicines than in countries that have pricing regulation (Simoens and de Coster 2006). In countries with free market pricing, the price difference between originator and generic medicines tends to be higher than in countries with pricing regulation (Adriaen, De Witte et al. 2007)

Generics offer significant cost-saving opportunities and play a key role in stimulating innovation through increased competition. The ability to achieve and sustain a high volume is the most important factor for generics as suggested by findings in Chapter 4. Generic firms offer more competitive prices if they can capture a higher share in the market, which drives the generic-branded price ratio down. These results imply that demand-side policies carry significant importance to ensure higher volumes for generics by encouraging physicians to prescribe low-cost medicines and pharmacists to substitute generic medicines unless indicated otherwise by the physician. Supply-side policies directed at generics will not be enough to promote generic entry. The slowdown in the economy and the on-going pressure on budgets is expected to push governments to promote generics (and increasingly biosimilars) more aggressively, through eased generic entry, generic substitution, and physician incentives for generic prescribing.

Finally, both the "Innovation through generics" timetable in the European Parliament in 2008 (Simoens 2008) and the Inquiry the DG Competition on the competitiveness of the pharmaceutical sector identified the key importance of eradicating shortcomings in current patent and registration systems to allow quicker generic entry following patent expiry (DG Competition 2009). The Sector Inquiry also foresees that use of specific strategies (e.g. settlements where originator pays generics to limit their entry) by originator companies to delay generic entry will be subject to scrutiny if deemed to be anti-competitive. Although these factors have not been included in the analysis in this thesis, they clearly constitute potential improvement areas in the European generics policy-making. Following a stick approach, audits or periodic industrial competitiveness analysis can be used to overcome some of these strategic barriers. Alternatively, following a carrots approach, incentives other than patents for pharmaceutical innovation can be developed to overcome some of these strategic barriers.

Prizes, granting a reward with fixed royalties, restricting the rights of the patent holder in cases of research funding by public institutions are some of the alternative ways of pharmaceutical R&D financing that have been suggested to overcome the insufficines of the current intellectual property rights (IPR) systems. Similarly, the current IPR system can be improved to improve quality of patents by making the requirements for novelty and non-obviousness stricter, which can partially overcome the evergreening patent strategy of branded firms trying to block generic entry (Rovira 2009). Such an approach may reduce litigation and uncertainty to all stakeholders.

5.5 Limitations and Further Research

The main limitation in this thesis is that survival times are estimated with respect to the first global launch of a new molecule or generic copy. The delays therefore do not capture variations in market authorization dates, pricing and reimbursement procedures and company strategies to delay launch due to profit spillover concerns in the on-patent sector. However, this approach still provides insight into the magnitude of the effects of various risk factors in explaining the international variation in launch dates for new molecules and first generic products. Regulatory organizations have increasingly harmonized the requirements for marketing approval. FDA and EMEA increasingly share information about new drug candidates as the pharmaceutical industry continues to become a global industry. The sub-analysis for centrally approved molecules in Chapter 2 shows that even if variation due to marketing authorization across markets is singled out, different pricing and reimbursement procedures result in different market access times for new molecules. Ideally, data on authorization dates and pricing and reimbursement approval would allow explaining the exact nature of the delays in each market.

Similarly, delays do not capture the impact of country-specific patent or SPC protection expiry dates and heterogeneity in local legislations regarding patents[117]. Availability of patent expiry dates would enable to characterize the monopoly period during which the originator develops brand loyalty. The relative delay of the originator molecule in each market, however, is used to control for the reduced exclusivity period in each market. Furthermore, branded firm strategies employed to delay generic entry such as authorized generics cases are ignored. Although authorized generics have more serious implications in the US market due to the exclusivity offered to the first generics, which is not the case in Europe, the analysis can be extended to investigate the impact of branded firm strategies on the timing of generic adoption.

The price data used in this analysis represents ex-manufacturer prices rather than actual prices paid by the government, third-party insurer or patients. Ex-manufacturer prices are the relevant prices when investigating launch strategies of pharmaceutical corporations as they determine profits of the industry. However, in most markets both innovator and generic companies offer significant discounts off these list prices. IMS data does not take into account discount practices (Simoens 2007). In particular,

[117] Patent validity and infringement issues are handled by different rules in each country; this increases financial costs as well as time burden on the generic manufacturers

variations in generic-company discounts offered to retail pharmacists may affect the incentives for substitution and the duration of the negotiation process. The analysis has tried to avoid issues of endogeneity by using lagged price and market size variables (also, the moving average over the last four quarters is used). The empirical analysis could be extended to include discounts and try alternative specifications to endogenize prices and entry.

In the context of generic entry, further research can be carried out to identify determinants of relative generic-branded medicine price levels and to estimate price sensitivities in individual markets, the main drivers of the market share captured by generics.

Finally, price controls and lower prices were found to discourage timely adoption both for new molecules and for generics. To what extent delayed or reduced entry affects total societal welfare cannot be inferred from the analysis in this thesis and could be explored as a future research question.

APPENDICES

APPENDIX A: Appendix to Chapter 1

Appendix A.1: Anatomic Therapeutic Classification

The ATC classification system divides drugs into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties. The drugs are divided into fourteen main groups (1st level), with one therapeutic subgroup (2nd level). The third and fourth levels are pharmacological/chemical therapeutic subgroups and the fifth level is the chemical substance. Classification in the IMS database is product based as defined by EphMRA[118]/ PBIRG classification, which is based on drug indication and use.

Table A.1 ATC Classifications

ATC Level	*Coding*	*Grouping*	*Example*
ATC1	1 Letter	Anatomical	A: Alimentary tract & metabolism
ATC2	2 Digits	Therapeutic	A10: Drugs used in diabetes
ATC3	1 Letter	Pharmacological	A10B: Glucose lowering drugs
ATC4	1 Letter	Chemical Subgroup	A10BA: Biguanides
ATC5	2 Digits	Chemical Substance	A10BA02: Metformin

Source: (EphMRA/PBIRG 2009; Danish Medicines Agency 2010)

Table A.2 ATC1 Categories

ATC1	*Category*
A	Alimentary tract and metabolism
B	Blood and blood forming organs
C	Cardiovascular system
D	Dermatologicals
G	Genitourinary system and sex hormones
H	Systemic hormonal preparations, excluding sex hormones and insulins
J	Anti-infectives for systemic use
L	Anti-neoplastic and immuno-modulating agents
M	Musculoskeletal system
N	Nervous system
P	Anti-parasitic products, insecticides and repellents
R	Respiratory system
S	Sensory organs
V	Various

[118] European Pharmaceutical Market Research Association http://www.ephmra.org/

Appendix A.2: Expenditure on Health and Pharmaceuticals

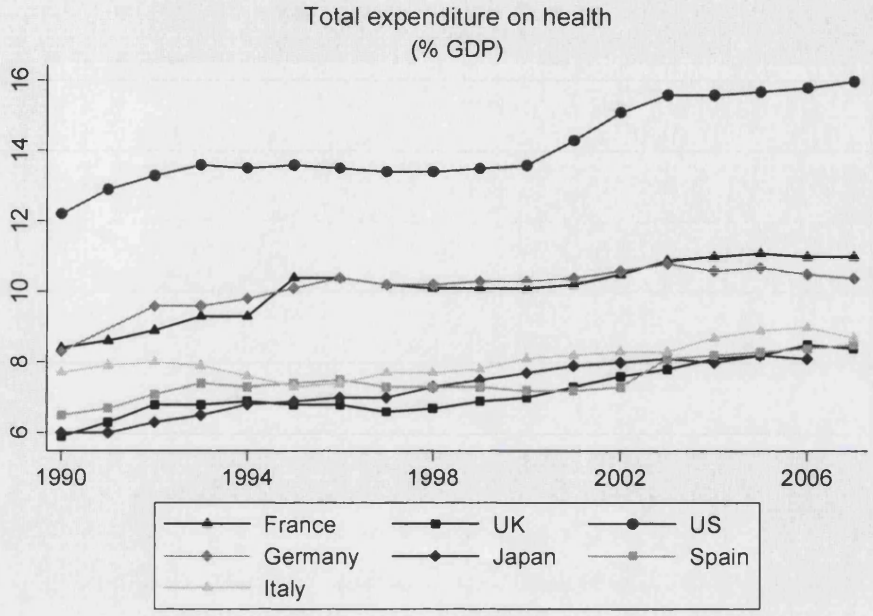

Figure A.1 Total expenditure on health (% of GDP)

Source: OECD Health Data 2009

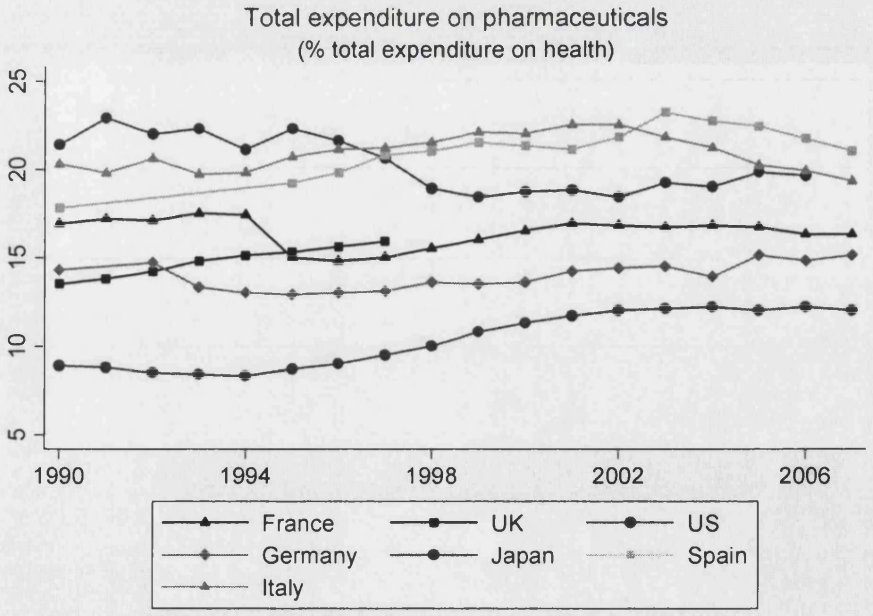

Figure A.2 Total expenditure on pharmaceuticals and other medical non-durables, % total expenditure on health (Source: OECD Health Data 2009)

Appendix A.3: Pharmaceutical Pricing and Reimbursement (P&R) in US-EU5

Throughout 1990s, both the US and the EU have witnessed increased efforts to accelerate and harmonize the regulatory approval process. Prescription Drug User Fee Act in 1992 required companies to pay user fees as part of their submissions for regulatory review which enabled increasing the review capacity and thus shortening the duration of the review process. FDA Modernization Act in 1997 provided a "fast track procedure" to facilitate the development and expedite the review of products intended for the treatment of serious or life-threatening conditions and with a potential to address unmet medical needs for such conditions. The EU established the EMEA (European Medicines Agency) in 1995 for the scientific evaluation of applications for European marketing authorization for medicinal products. Under the centralized procedure, companies submit a single marketing authorization application to the EMEA. Once granted by the European Commission, a centralized (or 'Community') marketing authorization is valid in all EU and EEA-EFTA states (Iceland, Liechtenstein and Norway)[119].

The centralized EU procedure is compulsory for all medicinal products derived from biotechnology and other high technology processes, all human medicines intended for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, autoimmune and other immune dysfunctions, and viral diseases, and all designated orphan medicines intended for the treatment of rare diseases. If the product does not belong to any of these categories, companies can submit an application for a centralized marketing authorization to the EMEA, provided the medicinal product constitutes a significant therapeutic, scientific or technical innovation, or the product is in any other respect in the interest of patient health[120]. The EMEA centralized procedure has been indicated to speed up the review process[121]. The Tufts Centre for the Study of Drug Development reported that European approval of new biotech drugs outpaced US approvals by 35 days during the period 1995-1999122. The centralized procedure has increased the role of pricing and reimbursement in launch delays since differences due to regulatory approval are eliminated.

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[119] EEA-EFTA: European Economic Area-European Free Trade Association

[120] http://www.emea.europa.eu/

[121] http://www.rsc.org/chemistryworld/Issues/2007/June/Europespeedsmedicinestomarketunderrevisedrules.asp

[122] csdd.tufts.edu/_documents/www/Doc_309_12_892.pdf

A second way to obtain marketing authorization in the EU is through the "mutual recognition procedure" whereby the originator submits for approval in one country and files for recognition in other countries. If the rapporteur country grants approval, the drug is approved automatically in reference countries unless an objection is made within 90 days.

In free-priced markets like the US, UK or Germany, branded pharmaceutical products can be launched after marketing authorization is granted; however, in other markets, pharmaceutical manufacturers may face additional hurdles following the review process of safety and efficacy data. Most OECD countries demand price approval and/or prior approval of eligibility for reimbursement before the product is commercialized (Jacobzone 2000). The latest trend is the increasing importance of the fourth hurdle, i.e. demonstration of cost-effectiveness, for drug reimbursement or for obtaining a price premium.

The following sections provide more detailed country-specific information on P&R in the US-EU5.

A.3.1 United States

The US market is highly fragmented in terms of the variety of payers. Healthcare is covered predominantly by private health insurance sponsored by employers (58%), and federal-sponsored plans of Medicaid and Medicare for the poor and the elderly respectively. The federal government does not provide health insurance coverage to all through a centralized scheme as in other European markets. Medicare and Medicaid are the largest government-funded payers providing coverage for more than 60 million individuals (Sullivan, Watkins et al. 2009). As of 2009, approximately 15% of the US population remains uninsured which results in poor health outcomes for this section of the population[123].

Pharmaceutical Pricing

Due to the absence of a government-sponsored universal health insurance plan and the variety of schemes for coverage, the federal government does not regulate the prices of pharmaceuticals. Pharmaceutical prices are determined predominantly by the free market. Free pricing has allowed manufacturers to capture higher margins in the US compared to

[123] http://www.census.gov/hhes/www/hlthins/hlthin08/hlth08asc.html

other markets. Drug price differentials between the US and other countries have become a highly debated political issue in the US.

US drug prices depend on the health insurance coverage of individuals, competition between substitute products including generics, market size, cost of R&D and price sensitivity of payers (large buying groups have influence through discount and rebate programs). Pharmacoeconomics and parallel importing may also affect pricing decisions in the US pharmaceutical market (Seget 2009), (Seget 2003), (Business Insights 2009b). Large buyers such as hospitals, managed care organizations, Medicaid and Medicare have a substantial bargaining power. In addition, there is de facto price regulation in the case of federal purchases such as the Veterans Health Administration and the Medicaid programme; pharmaceutical companies price drugs for these organizations on a negotiated discount basis (OECD 2008), (Seget 2003).

Pharmaceutical Reimbursement

Reimbursement controls in the US play a major role due to the lack of price controls in containing costs and determining revenues of pharmaceutical manufacturers. The main reimbursement-related cost containment measures include preferred drug lists (formularies[124]), and cost-sharing in the form of deductibles[125], coinsurance and tiered co-payments (Seget 2003),(Business Insights 2009b).

Both private and public payers use formularies as a major reimbursement control. Drugs excluded from formularies are not reimbursed. Formularies aim to achieve savings by encouraging cost-effective or low-cost drug use as well as obtaining rebates from companies. Patient copayment levels in formularies are determined based on drug's patent status, cost and clinical effectiveness. Copayment levels are tiered, usually between 10-20%, depending on whether the drug is a generic, preferred branded, non-preferred branded or specialty drug. Patients are given incentives to choose less expensive drugs in the lower tiers through lower copayment levels. OTC (over-the-counter) drugs are excluded from reimbursement.

[124] List of drugs preferred by a particular health plan or employer prefers

[125] Out-of-pocket payment threshold made before benefits become reimbursable

Pharmacoeconomics

Pharmaceutical companies are not explicitly required to submit cost-effectiveness evaluations neither for US regulatory approval nor for price negotiations with private or public payers. However, some costly drugs are supported by such evaluations to defend high prices. In addition, several public and private agencies produce or use health technology assessment (HTA) reports[126]. Currently there are no established frameworks and thresholds for cost-effectiveness evaluations (Seget 2009). Multi-state HTA programs could be redundant and inefficient, and result in inconsistent coverage policies between states. Main federal funding body for publicly available HTAs in the US is the Agency for Healthcare Research and Quality (AHRQ). Since 2003, AHRQ supports the generation of systematic evidence reviews by Evidence-Based Practice Centers to assess the effectiveness, comparative effectiveness, safety, and rarely the cost-effectiveness of medical technologies and interventions. The relevance of the AHRQ reports to inform coverage decisions in the private sector has been limited.

Generic Substitution

The US healthcare system has benefited from substantial cost savings due to increased generic use and generic competition. Generics accounted for 63-69% of all dispensed prescriptions in the US in 2007 and 2008 respectively, which is higher than in any of the EU5 markets (Seget 2009), (Business Insights 2008)[127]. Individual states may have different generic substitution regulations. However, many states indicate that drugs the FDA deems to be equivalent (Orange Book lists) may be substituted, or alternatively that drugs the FDA does not list as equivalent cannot be substituted. Positive formulary states identify generics that can be substituted while negative formulary states identify generics that cannot be substituted. Some states simply allow substitution for pharmaceutically equivalent products[128].

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[126] For example, the Medicare Coverage Division within the Centre for Medicare and Medicaid Services (CMS) is responsible for undertaking or commissioning HTA reports to support considerations regarding national coverage decisions. Many state Medicaid programs support state-sponsored HTA activities for pharmaceuticals.

[127] The US generic market is the world's largest generics market, with a size of $25 bn in 2007.

[128] http://www.uspharmacist.com/content/t/generic_medications/c/9787/

A.3.2 EU5

Unlike in the US, pharmaceutical expenditure in the EU is mostly reimbursed by social security systems, which increases the role of governments in the determination of pharmaceutical prices. The European market is characterized by significant price dependencies between member states. The principle of exhaustion of rights allows individuals or firms within the EU to trade goods across borders and prevents the proprietor from using those rights to interfere with any subsequent commercialization of the goods in question.

In the case of medicines, parallel importation[129] is allowed if the product imported is identical or sufficiently similar to one already authorised for sale in the Member State of destination[130] . Parallel importation cannot take place from within the EU to countries outside the EU since the idea of international exhaustion has been rejected by the European Court of Justice (Ganslandt and Maskus 1999). The introduction of the centralized procedure for market authorization has further facilitated parallel trade since standardized drug dosages are approved in all Member States. Package or labelling differences, which previously hindered parallel trade by increasing a trader's costs of repackaging and labelling, were reduced.

The pricing and reimbursement of medicinal products in the EU has been regulated at the supranational level by the Transparency Directive since 1989. The Directive, however, does not affect national policies on price setting and on the determination of social security schemes, except for the stipulation of the main transparency objectives that guarantee public access to information on pricing and reimbursement[131]. This has resulted in a variety of pricing and reimbursement schemes across the EU.

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[129] Parallel imports are products imported from a Member State with a lower price to another Member State where the product is sold at a higher price, outside the manufacturer's or its licensed distributor's formal channels.

[130] http://ec.europa.eu/enterprise/regulation/goods/medicines_en.htm

[131] These include: 1. Adopting decisions within a limited time frame; 2. Making decisions on objective and verifiable criteria; 3. Notifying decisions to the applicant and publishing the rationale behind the decisions; 4. Ensuring adequate judicial procedures for appealing against the decisions . This has resulted in diverse pricing and reimbursement schemes across the Member States.

Pharmaceutical pricing and reimbursement schemes in the EU5 are summarized in Table A.3. Germany and the UK have traditionally focused on controlling demand with devolved budgets, i.e. constrained physician prescribing (Businessweek 2009). Branded pharmaceuticals are freely priced in Germany and the UK, except for company-level profit controls in the UK through the PPRS. France, Italy and Spain, on the other hand, have focused mainly on price controls. Branded drug prices in France, Italy and Spain are subject to statutory control through negotiations in France and Italy (before 2004 price determination was based on average EU prices) and cost-plus pricing in Spain. All three markets employ both internal and external reference pricing systems[132] for price setting. Generic prices are controlled across all five markets in the EU5 with minimum discount requirements over originator prices.

All markets in the EU5, except for the UK, use reference-pricing systems for reimbursement decisions[133]. Germany, UK and Spain have negative lists whereas France and Italy employ positive lists. Italy and Spain have regional autonomy in reimbursement of prescription fees and generic substitution. Cost-effectiveness evaluations are used in reimbursement decisions in Germany and the UK for selected drugs through IQWiG and NICE respectively , as well as informally in other markets (Seget 2009).

[132] Reference Pricing is a mechanism that controls drugs reimbursed by third party payers. Under a reference pricing system (RPS), drugs are clustered into reference groups based on chemical (active ingredient), pharmacological (comparable active ingredients) or therapeutic equivalence (similar therapeutic effects). In general, the reference price is the reimbursement price and the patient pays the difference between the actual retail price and the reference price. If the price is below the reference price and there is a copayment system, the patient pays a fraction of the reference price under a copayment system. Reference pricing aims to increase generic use and decrease pharmaceutical expenses by controlling the price at which the drugs are reimbursed.

[133] Although not shown in the table, all markets have exemption provisions linked to age, income and disease for prescription fees and copayments

Table A.3 Pharmaceutical P&R and Rational Drug Use in the EU5

	France	*Germany*	*Italy*	*Spain*	*UK*
Pricing: Outpatient Reimbursable Drugs	Price negotiations	Free pricing	Price negotiations	Cost-plus pricing + External referencing	Free pricing + profit control
Pricing: Generic Drugs	Profit control	Free pricing with 10% discount for sickness funds	Minimum 20% discount on original	Minimum discount	Price control for most drugs
External Ref Pricing	Innovative drugs only referenced with Germany, Italy, Spain and UK	No	Yes, based on the average of selected EU markets	Yes, based on EU average	No
Internal Ref Pricing	Yes	For reimbursement only	Yes	Yes	Limited
Positive/Negative Lists	Positive List	Negative List	Positive List	Positive and Negative List	Negative List
Reimbursement Levels	100%, 65%, 35%	100%	100%	90% and 60%	100%
Reference Pricing System	Limited (ATC5)	Yes (ATC4-5)	Yes (ATC5)	Yes (ATC5)	No
Out-of-Pocket Expenses	0%, 35%, 65% coinsurance	10% copayment in the range €5-€10; no copay if drug price is 30% below the reference price	Regional prescription fee	0%, 10%,40% co-insurance up to a maximum per item	Flat prescription fee of £7.20
Generic (INN) prescribing	Encouraged, GPs must prescribe at least 15% a year	Indirectly encouraged via reference pricing classes	Some via reference pricing classes	Encouraged and rising with regional variations	GPs prescribe generics by INN
Generic Substitution	Substitution extended but physician can overrule	Substitution obligatory unless physician overrules	Limited (indicative) substitution rights	Substitution allowed but requires physician consent; also through RPS	Substitution allowed if physician has prescribed by INN
Cost-effectiveness evaluations	No	Yes, for selected drugs through IQWiG	Applied for price negotiations only	No	Yes, for selected drugs through NICE
Guidelines	HAS Guidelines	IQWiQ-GBA Guidelines	AIFA Guidelines	Significant variations across regions	NICE Guidelines

Budgets	Target budgets monitored by health insurance delegate	Target volumes for individual practices negotiated at regional levels	Budgets set by local health authorities	Drug budgets subject to fixed growth rates and paybacks	PCTs and GP practices given a budget
Price Cuts	12.5% brands and 7% generics on drugs in the market for 18 months	Price freeze	Price cuts	Since 2006, price cuts of 20% on drugs marketed 10 years	PPRS
Clawbacks	National, therapy and product specific price volume agreement	Mandatory annual rebates in cash	Price volume agreements based on annual expenditure ceilings	Clawbacks % of annual sales based on total sales value	% of pharmacy discounts clawbacked to NHS

INN: International Non-proprietary Name of the active ingredient

Source: (Vogler 2008; Seget 2009)

A.3.2.1 France

The French population is almost universally covered (99% of the population) by statutory health insurance, a branch of the wider social security system. The share of public pharmaceutical expenditure in total pharmaceutical expenditure was 69% in 2006.

Pharmaceutical Pricing

Ex-factory prices in France for reimbursable products are negotiated between the Economic Committee for Health Care Products (CEPS) and pharmaceutical manufacturers. Prices mainly depend on the improvement in medical service (Amélioration du service medical rendu, ASMR[134]), price of comparator products, sales forecasts, target population, conditions for use, and prices in the UK, Germany, Italy and Spain for innovative products. Non-reimbursable drugs, drugs for hospital use and OTC products are free-priced. Wholesale margins, pharmacist margins and pharmacy retail prices are subject to regulation. Only innovative products that offer major, significant or moderate therapeutic progress (ASMR I, II or III) are subject to external referencing and are priced above the cheapest price in the remaining EU-5 for 5 years after inclusion in the positive list.

[134] ASMR is a five-level scale that evaluates the level of medical service delivered by a new drug (I: major therapeutic progress; II- significant progress in terms of efficacy/side effects; III- moderate progress in terms of efficacy/side effects; IV- minor progress in terms of efficacy/clinical usefulness/side-effects; V- no therapeutic progress)

Pharmaceutical Reimbursement

Pharmaceutical manufacturers have to apply for inclusion on positive lists in order to obtain reimbursement by the mandatory health insurance. There are two positive lists: one for reimbursable retail channel drugs and one for hospital drugs. Reimbursement by the Health Insurance Funds is conditional on an improvement in medical service (ASMR level) or savings in the cost of treatment offered by the new pharmaceutical product. Reimbursement rate depends on the medical service and improvement of medical service offered by the product, and the clinical benefit. There are three different rates of reimbursement: 100% for severe, chronic diseases such as cancer; 65% for drugs with major clinical benefit and 35% for all others. The difference between the retail price and the rate reimbursed is paid out-of-pocket by the patient.

Pharmacoeconomics

Economic evaluations are increasingly gaining importance in pricing negotiations for new drugs, in particular for drugs that claim a price premium, although the submission of such evaluations is not yet mandatory. Since 2008, National Authority for Health (HAS, Haute Autorité de Santé) has been given the responsibility to assess the most efficient therapeutic strategies and develop recommendations accordingly. However, how pricing and reimbursement of pharmaceuticals will be affected by this decision remains to be seen[135].

Generic Substitution

Generic substitution is allowed on a voluntary basis since 1999 and promoted through higher margins as a financial incentive to pharmacists (pharmacists are remunerated the same value both for branded and generic products). Physicians are encouraged to prescribe by INN name as the rise in physician visit prices depends on pharmaceutical expenditure levels. Generic drug use is promoted by the government and health insurance to reduce public expenditure. Generics with prices 50% lower than the originator are automatically included in the reimbursable drug list (Liste Sécurité Sociale et Collectivités).

A.3.2.2 Germany

The German healthcare system has adopted mandatory Social Health Insurance (SHI) with more than 200 competing sickness funds and a private-public mix of providers. About 85%

[135] http://www.ispor.org/HTARoadMaps/France.asp#1

of the population was covered by comprehensive SHI in 2005. The share of public pharmaceutical expenditure in total pharmaceutical expenditure was 71.3% in 2005.

Pharmaceutical Pricing

Ex-factory prices are freely determined by manufacturers except for temporal prize freezes. There are no negotiations involving governmental agencies, direct price or profit controls employed. There is, however, regulation at the wholesaler and pharmacist level through fixed mark-ups for prescription drugs. Price setting by companies is affected by reimbursement regulations through the reference pricing system.

Pharmaceutical Reimbursement

Germany does not have a positive list for pharmaceuticals that are reimbursed by the Social Health Insurance; every prescription drug that accesses the market is fully reimbursed with the exception of drugs for trivial diseases such as common colds and life-style drugs (Vogler 2008). Reimbursement is independent of patient subgroups or indications. Co-payments are set at 10% of the drug price. Drugs with prices 30% below the reference price are not subject to co-payment. Upper limits for cost sharing exist for the poor and individuals with high healthcare costs.

Regulation of reimbursement through the reference price system (RPS) acts as an indirect price control mechanism since 1989. The reference price system dictates an upper limit for sickness fund reimbursements, and the remaining part is covered by the patient as an out-of-pocket payment. Reference groups usually are set at the active ingredient (ATC5) level but can include several active ingredients that are pharmacologically or therapeutically comparable. Not all drugs are subject to the RPS. If the efficacy or safety of a drug is superior to existing alternative drugs, prices can be set freely without any regulatory control; otherwise, prices are subject to reference pricing.

Pharmacoeconomics

Since 2004, the Institute for Quality and Efficiency (IQWiG) provides assistance with the therapeutic benefit assessment of new products to determine reimbursement status. IQWiG also ensures the reimbursement for drugs already on the market is correct through retrospective evaluations. Since 2007, IQWiG carries out cost-benefit assessments for drugs

with therapeutic improvements, which are used to provide recommendations for a maximum reimbursement price for innovative drugs that are not included in reference pricing. In contrast to other HTA agencies such as NICE, IQWiG does not use the incremental-cost-effectiveness-ratio approach, but uses the efficiency frontier approach. Although Germany employs free-pricing, drugs with a negative cost-benefit-assessment may be subject to maximum prices[136].

Generic Substitution

Generics in Germany are subject to the same rules as original products. Generic use is encouraged in a number of different ways. Generic substitution is obligatory for pharmacists unless substitution is explicitly excluded on the prescription by the physician. Sickness funds may contract with generic manufacturers and pharmacies for generic substitution, which has increased the negotiating power of sickness funds for rebates from generic manufacturers. Generics companies have to give a 10% rebate on generic preparations to sickness funds since 2006.

Physicians in Germany were subject to drug budgets to control pharmaceutical expenses during 1993-2001. Since 2002, practice-specific prescription targets are employed; sickness funds have accepted target volumes and provide prescription feedback to SHI affiliated physicians. In 2007, a cap on average prescription costs was introduced for highly prescribed substances. Physicians exceeding the target by more than 10% have to reimburse the deficit. These measures have improved generic prescribing.

[136] http://www.ispor.org/HTARoadMaps/Germany.asp

A.3.2.3 Italy

Health coverage in Italy is provided by the National Healthcare System SSN (Servizio Sanitario Nazionale) with a decentralized system. Although pricing and reimbursement of products is mainly decided on the national level, regions can decide upon patient copayments resulting in price difference of pharmaceuticals for the patients across the country. The share of public pharmaceutical expenditure in total pharmaceutical expenditure was 67.13% in 2005.

Pharmaceutical Pricing

Until 2004, prices in Italy used external reference pricing to set prices with respect to the average European prices. Since 2004 prices in Italy are determined by negotiation based on several factors that include the degree of innovation, prices and consumption data in other EU countries, sales volume and market share estimates, epidemiology, target population of the drug, risk-benefit ratio compared to comparator products, improvements in quality of life and available pharmacoeconomic data.

The level of innovation within a therapeutic category for new products is classified as important, moderate and mild. Generally, premium pricing requires an important innovation rating; parity pricing requires at least a moderate innovation rating, with any mild innovations likely to result in a price discount.

Pharmaceutical Reimbursement

Pharmaceutical companies apply for reimbursement on the National Pharmaceutical Formulary (PFN Prontuario Farmaceutico Nazionale). Criteria for including a new product on a positive list for reimbursement includes: product-specific criteria (therapeutic value, safety, alternatives, prescription status, patent status); economic criteria (cost-effectiveness, reference price, forecasts); and disease-specific criteria (severity, unmet needs, patient base). Prescription pharmaceuticals on the positive list are fully reimbursed. Non-reimbursed products can be freely priced. Technical and pharmacological innovations, i.e. new molecular entities and novel modes of action, are granted provisional reimbursement approval subject to demonstrated therapeutic need; disease relevance to public health interests; and defined timelines for post-marketing data. For off-patent drugs, only the

lowest priced version of the same active ingredient is reimbursed. Patients have to pay fixed prescription fees at the regional level and any copayments due to the internal reference pricing system.

Pharmacoeconomics

There are no formal requirements for cost-effectiveness evaluations or budget impact analysis for pricing and reimbursement decision making in Italy. However, such evaluations are used widely in price negotiations and reimbursement decisions, especially for innovative products seeking premium prices.

Generic Substitution

Generic substitution by the cheapest off-patent generic is encouraged unless prohibited by the physician. Generics have to offer a price discount of 20% with respect to the price of the originator product.

A.3.2.4 Spain

Healthcare in Spain is provided by the National Health Service SNS (Sistema Nacional de la Salud) and is decentralized to the seventeen autonomous regions that have full control of budgets and competence regarding public health (Vogler, Espin et al. 2009). The system provides universal coverage with general taxation financing. The central government, however, maintains the responsibility related to pharmaceutical pricing and reimbursement[137]. Regions have a degree of freedom to impose their own pharmaceutical price caps or cost-containment targets. The share of public pharmaceutical expenditure in total pharmaceutical expenditure was approximately %72 in 2007 (OECD 2008).

Pharmaceutical Pricing

In Spain, only reimbursed drugs are subject to price regulation; non-reimbursable prescription-only pharmaceuticals are freely priced (subject to price approval). Products excluded from public financing are put on the negative list and are subject to free pricing (there are two negative lists from 1993 and 1998 respectively). The two delistings in the

[137] http://www.ispor.org/HTARoadMaps/Spain.asp

Spanish pharmaceutical system in 1993 and 1998 were not effective in containing expenditures as excluded drugs were of low therapeutic value and was dampened by strategic drug substitution for which reimbursement was maintained (Costa-Font and Puig-Junoy 2007).

Spain employs external referencing and 'cost plus' pricing, which determines maximum drug prices based on manufacturer costs (R&D expenses, manufacturing and marketing expenditure) plus a premium. The maximum return, typically between 12-18%, depends on the relative innovativeness of the new product and the availability and prices of equivalent prices as well as external price comparisons and potential volume and value of sales. Other supplier-oriented cost-containment measures that have been applied include negative lists, internal reference pricing, price cuts, encouragement of generic substitution, and pharmacy discounts.

Generics are subject to the same regulations as other reimbursed prescription medicines. Generics in the reference price system must be priced at, or below, the reference price level although there are no official guidelines (Habl, Antony et al. 2006). For competitive reasons most generics manufacturers prefer to price their products below the reference price level (Vogler, Espin et al. 2009). Wholesaler and pharmacy margins are statutorily fixed for all reimbursable and non-reimbursable pharmaceuticals.

Pharmaceutical Reimbursement

Reimbursement decisions precede the price decision, as non-reimbursable drugs are not subject to price controls. Reimbursement criteria in Spain include the severity of the disease; priorities of different population groups; therapeutic value, degree of innovation and efficacy of the drug; budget impact for the SNS compared to corresponding products; and availability of similar cheaper alternatives. Four different reimbursement levels are available: 100% (hospital drugs and ambulatory drugs for retirees), 90% (chronic disease drugs), 60% and 0% (drugs on the negative lists).

The reference pricing system in Spain was adopted in 2000, with some modifications in 2004 and 2006. Reference price groups are comprised of pharmaceuticals with the same active substance (ATC5), form and route of administration and have at least one generic version. Reference prices are based on the arithmetic mean of the three cheapest drugs in

terms of cost per treatment per day for each route of administration[138]. Since 2007, these products no longer have to be produced by different companies. Generic prices have to be at or below the reference price level. Different from the other markets, Spanish reference pricing system sets a maximum price level, rather than the maximum reimbursed price. If a pharmaceutical has a higher price than the reference price level, the pharmaceutical company pays the difference and the patient only pays the copayment for the reference price. Unlike in other markets, patients are not offered the option of paying the difference between the reference price and the retail price of pharmaceuticals (Vogler, Espin et al. 2009). After the Spanish healthcare system was decentralized in 2002, regions focused on demand-side measures to contain costs and introduced their own regional maximum price reimbursement schemes, which were withdrawn with the modified reference price system in 2007.

Pharmacoeconomics

Submission of pharmacoeconomic studies by manufacturers is not mandatory; however, companies submit such studies to show the product's budgetary benefits for pricing and reimbursement decisions. It is not clear to what extent pharmacoeconomic studies affect pricing and reimbursement decisions. A national HTA agency and seven regional HTA agencies coexist in the country. Regional HTA agencies are responsible for producing information on the efficacy, effectiveness, safety and efficiency of new health technologies. Proposals published for standardisation of economic analysis of health technologies have not yet received mandatory status. The new law in 2006 requires companies to provide all information regarding the technical, economic and financial aspects of new products, but no explicit rules have been indicated for pharmacoeconomic studies (Vogler, Espin et al. 2009).

Generic Substitution

Generic substitution is allowed and is obligatory for pharmaceuticals under the RPS when the generic has the lowest price unless explicitly excluded by the physician. The new pharmaceutical law of 2006 promotes prescribing by the active ingredient name (INN). For INN prescriptions, the law requires that pharmacists dispense the pharmaceutical with the lowest price, and the generic version if prices are same with a generic one.

[138] Products with ex-manufacturer prices below 2€ are excluded from reference pricing.

A.3.2.5 UK

The English National Health Service (NHS) offers universal coverage for UK residents. Private insurance coverage in the UK is relatively low, compared to countries such as the US; however, the role of private healthcare is increasing in the form of healthcare financing and delivery[139]. The share of public pharmaceutical expenditure in total pharmaceutical expenditure was 75% in 2007 (OECD 2008).

Pharmaceutical Pricing

Branded prescription drug prices are indirectly controlled by the Pharmaceutical Price Regulation Scheme (PPRS), a scheme that tries to balance the need NHS cost-containment and provision of incentives to the pharmaceutical industry for future R&D. The PPRS restricts the return on capital that can be made from sales to the NHS to 21% of a company's total NHS sales. Pharmaceutical companies earning excess profits have to reduce their prices or make a repayment to the Department of Health (DoH).

The UK has a free pricing system for on-patent pharmaceuticals that enter the market following the grant of a marketing authorisation for a new active substance or for line extensions of these products within 5 year of the grant of the original authorization. DoH's price agreement is required for any new product that has not been subject to a new active substance marketing authorisation. DoH accepts the price based on the price of other presentations of the same medicine or comparable products, forecast sales and the effect on the NHS bill, and the clinical need for the product. NHS list price of existing products is subject to the DoH's agreement as well.

The most recent 2009 PPRS emphasizes value-based pricing and proposes a more systematic use of patient access schemes to improve patient access to medicines which have not initially been assessed as cost or clinically effective by NICE. New and more flexible pricing arrangements in the 2009 PPRS enable manufacturers to supply drugs to the NHS at lower initial prices, with the option of increasing prices if value is proven later. In addition, more flexibility is introduced for price increases of drugs already in the market subject to NICE recommendations (Department of Health December 2008).

The system for pricing generics is different from that for branded medicines. Generic prices are set at prevailing market levels, plus a margin counted towards pharmacy remuneration. Maximum Price Scheme was introduced in 2000 to limit reimbursement

[139] http://www.ispor.org/HTARoadMaps/UK.asp

prices of most commonly dispensed generic medicines. This scheme was replaced in 2005 by a system based on average manufacturer prices after discount.

Pharmaceutical Reimbursement

In the NHS, restrictions are placed on what can be prescribed; any pharmaceutical on the limited list is excluded from National Health Service prescription. All items, which can be prescribed on the NHS, are fully reimbursable with a fixed copayment per item.

Pharmacoeconomics

The National Institute for Health and Clinical Excellence (NICE) provides independent guidance on the cost-effectiveness of new technologies and treatments as well as the existing technologies on the market since 2006. Currently pharmacoeconomic evaluations are not taken directly into account when setting prices, nor reimbursement status. However, technology appraisals carried out by NICE have an indirect impact on price. NICE guidance on whether a product should be used in the NHS highly depends on the price level of the pharmaceutical product. Submission of pharmacoeconomic evaluations is mandatory for all pharmaceuticals referred to NICE for technology appraisal (Vogler 2008).

The UK is the first market where innovative risk-sharing schemes for pharmaceutical reimbursement were applied in 2002. The NHS made an agreement with multiple sclerosis companies to reduce prices if cost-effectiveness targets were not met. Risk sharing agreements have involved caps on the length of reimbursement, manufacturer discounts and rebates for non-responding patients. The use of such risk sharing agreements has become more common in the UK over time and recently in Italy. The 2009 PPRS provides a framework for risk sharing and flexible pricing in the UK and is expected to increase the importance of such agreements in providing market access to high-priced innovative therapies in the UK.

Generic Substitution

Generic prescribing is encouraged but not mandatory; as of 2009, substitution at the pharmacy level is only allowed if prescribed by INN. However, in early 2010, generic substitution will come into effect, which will allow dispensing an equivalent generic medicine unless substitution is excluded by a physician. The introduction of generic substitution together with price cut provisions in 2009 and 2010 is expected to decrease NHS spending on branded medicines 5% per annum over the lifetime of the scheme.

APPENDIX B: Appendix to Chapter 2

Appendix B.1: Descriptive Tables and Results

Table B.1 Number of Markets Molecules Launched

# Markets Launched	Freq.	Percent	Cum.
1	969	21.09	21.09
2	432	9.4	30.5
3	346	7.53	38.03
4	285	6.2	44.23
5	247	5.38	49.61
6	200	4.35	53.96
7	165	3.59	57.55
8	160	3.48	61.04
9	134	2.92	63.95
10	128	2.79	66.74
11	131	2.85	69.59
12	125	2.72	72.31
13	115	2.5	74.81
14	108	2.35	77.17
15	112	2.44	79.6
16	126	2.74	82.35
17	121	2.63	84.98
18	163	3.55	88.53
19	192	4.18	92.71
20	335	7.29	100
Total	4,594	100	

Figure B.1 Histogram and kernel density of failure times

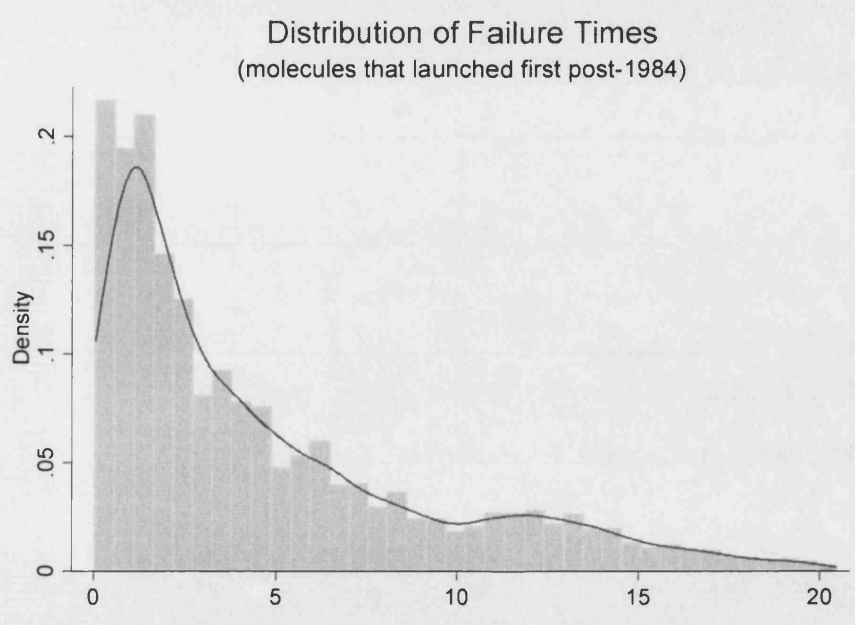

Table B.2 Number of Molecules by country and period of first global launch

	US&UK MOLECULES			
	[60-84)	[84-95]	[95-08]	Total
Australia	311	156	217	684
Austria	272	165	243	680
Belgium	265	136	166	567
Canada	332	159	218	709
Finland	236	158	245	639
France	305	172	233	710
Germany	325	175	257	757
Greece	263	163	210	636
Italy	296	168	239	703
Japan	260	124	132	516
Netherlands	259	163	219	641
Poland	297	163	210	670
Portugal	213	116	110	439
South Africa	306	161	168	635
Spain	264	138	153	555
Sweden	196	149	226	571
Switzerland	309	170	227	706
Turkey	253	156	178	587
UK	385	194	266	845
US	385	194	266	845

Table B.3 Mean and Median Launch Lags over Time

Country	*US & UK Molecules (Non-generic)*					
	1995-2008		1984-1995		1960-1984	
	Mean	Median	Mean	Median	Mean	Median
Australia	3.598(*)	1.752	8.146(*)	4.838	18.143(*)	12.252
Austria	2.181(*)	0.999	6.514(*)	3.42	19.254(*)	9.415
Belgium	5.720(*)	2.667	9.137(*)	3.666	19.791(*)	8.501
Canada	3.431(*)	1.336	7.402(*)	4	13.257(*)	6.084
Finland	2.259(*)	0.999	7.397(*)	3.337	22.804(*)	13.999
France	2.903(*)	1.585	6.482(*)	3.329	16.558(*)	6.585
Germany	1.444	0.668	4.703(*)	2.001	11.576(*)	3.001
Greece	4.138(*)	2.166	7.798(*)	4.58	22.250(*)	14.412
Italy	2.927	1.749	6.227(*)	3.584	16.019(*)	6.253
Japan	7.885(*)	6.582	12.441(*)	9.673	21.218(*)	11.414
Netherlands	3.042(*)	0.75	5.726(*)	1.837	19.158(*)	7.247
Poland	4.402(*)	3.001	9.395(*)	7.335	27.980(*)	26.497
Portugal	8.521(*)	13.254	12.884(*)	8.83	25.436(*)	19.162
S.Africa	5.590(*)	3.168	7.877(*)	4	21.776(*)	20.246
Spain	6.318(*)	2.667	10.117(*)	5.84	19.309(*)	7.077
Sweden	2.809(*)	0.747	8.311(*)	4.167	27.842(*)	27.83
Switzerland	2.964(*)	1.413	5.842(*)	2.828	12.799(*)	4.085
Turkey	5.701(*)	4	9.381(*)	6.834	25.803(*)	21.832
UK	1.27	0.75	3.151	1.914	8.817	3.083
US	0.665	0.001	3.602	2.664	10.052	7.666
OVERALL	3.829(*)	1.667	7.636(*)	4.085	18.823(*)	10.587

(*) largest observed analysis time is censored, mean is underestimated

Table B.3 presents the mean and median failure times in each country for molecules that first launched globally during 1995-2008, 1984-1995 and 1960-1984 respectively. The restricted mean times are reported, i.e. the area under the survival curve without exponentially extending the survival curve to zero. The median survival times correspond to the failure time when the probability of survival beyond t is 0.5, i.e. $S(t) = 0.5$.

Tables for Generic Molecules

Table B.4 Number of Generic Molecules by Period of First Launch

Country	*1960-1984*	*1984-1995*	*1995-2008*	*Total*
Australia	157	57	31	245
Austria	115	55	29	199
Belgium	110	45	18	173
Canada	172	64	35	271
Finland	115	51	29	195
France	132	59	27	218
Germany	170	71	40	281
Greece	130	55	22	207
Italy	139	57	27	223
Japan	146	41	21	208
Netherlands	131	61	31	223
Poland	162	68	30	260
Portugal	95	51	21	167
S.Africa	100	52	24	176
Spain	120	53	25	198
Sweden	85	50	27	162
Switzerland	123	51	16	190
Turkey	128	51	26	205
UK	214	90	46	350
US	214	90	46	350

Table B.5 Mean and median launch delays for generic molecules that launched in the US and UK

Country	1960-1984			1984-1995			1995-2008		
	Subjects	*Median*	*Restricted mean*	*Subjects*	*Median*	*Restricted mean*	*Subjects*	*Median*	*Restricted mean*
Australia	199	24.586	27.460(*)	85	16	15.446(*)	42	8.085	7.425(*)
Austria	207	33.418	31.961(*)	86	14.001	16.248(*)	45	7.915	7.877(*)
Belgium	210	39.086	33.843(*)	89	17.084	18.075(*)	46	.	10.052(*)
Canada	200	17.333	22.390(*)	86	10.242	12.981(*)	40	6.916	6.560(*)
Finland	200	31.496	31.367(*)	89	16	16.553(*)	44	7.417	8.098(*)
France	205	29.752	31.178(*)	87	15.663	15.912(*)	46	8.914	8.610(*)
Germany	191	15.168	20.877(*)	83	12.167	12.768(*)	44	5.081	6.060(*)
Greece	200	32.838	30.055(*)	85	15.253	15.215(*)	46	8.413	9.261(*)
Italy	176	27.083	28.294(*)	85	16.999	16.817(*)	46	9.339	8.374(*)
Japan	181	18.412	24.920(*)	88	22.412	18.784(*)	45	11.496	9.782(*)
Netherlands	191	32.832	32.053(*)	71	13.413	15.386(*)	42	6.418	7.451(*)
Poland	193	29.495	30.611(*)	84	11.086	13.114(*)	41	7.168	7.858(*)
Portugal	209	.	35.085(*)	86	16	15.922(*)	45	11.496	9.259(*)
S.Africa	154	31.247	32.282(*)	81	14.834	16.261(*)	42	8.832	8.911(*)
Spain	195	34.749	31.147(*)	83	13.919	16.110(*)	43	9.747	8.965(*)
Sweden	212	.	36.388(*)	90	15.001	16.578(*)	45	8.167	8.119(*)
Switzerland	201	29.248	30.654(*)	89	15.918	17.173(*)	45	.	10.530(*)
Turkey	209	28.413	29.481(*)	82	16.085	15.293(*)	39	9.832	8.767(*)
UK	194	18.168	18.619	80	11.25	10.596	42	4.252	4.486
US	197	13.67	14.767	79	9.752	9.754	41	4.504	5.224
total	3924	26.831	28.615(*)	1688	14.579	15.314(*)	869	7.833	8.117(*)

(*) largest observed analysis time is censored, mean is underestimated

Table B.5 presents the mean and median failure times in each country for generics that first launched globally during 1995-2008, 1984-1995 and 1960-1984 respectively. The restricted mean failure times correspond to the area under the survival curve without exponentially extending the survival curve to zero. The median survival times represent failure times when the probability of survival beyond t is 0.5, i.e. $S(t) = 0.5$.

Appendix B.2: Non-parametric Survival Analysis

In the context of survival analysis, main functions of interest are the survival function $S(t)$, the hazard function $h(t)$ and the cumulative hazard function $H(t)$. The survival function indicates the probability of surviving beyond time t or the probability that no failure event occurs prior to time t.

$$S(t) = \Pr(T > t) = 1 - F(t) = 1 - \int_0^t f(u)du$$

where T is a non-negative random variable that denotes the time to failure, $F(t)$ is the cumulative distribution function of failure time and $f(t)$ is the probability density function of failure time. The survivor function is a monotone, non-increasing function of time.

$S(t) \in [0,1]$,

$S(0) = 1$ and $\frac{\partial S(t)}{\partial t} < 0$.

Probability density function for the survival time is:

$$f(t) = \lim_{\Delta t \to 0} \frac{\Pr(t \le T \le t + \Delta t)}{\Delta t} = \frac{\partial F(t)}{\partial t} = -\frac{\partial S(t)}{\partial t}$$

where Δt is an infinitesimal interval of time and $f(t) \ge 0$.

The hazard function is defined as the instantaneous rate of failure. It is the limiting probability that the failure event occurs between time t and $t + \Delta t$ conditional on survival up to time t, divided by the interval length Δt.

$$h(t) = \lim_{\Delta t \to 0} \frac{\Pr(t \le T < t + \Delta t \mid T \ge t)}{\Delta t} = \frac{\Pr(t \le T < t + \Delta t)}{\Pr(T \ge t)} \cdot \frac{1}{\Delta t} = \frac{f(t) \cdot \Delta t}{S(t)} \cdot \frac{1}{\Delta t} = \frac{f(t)}{S(t)}$$

$$h(t) = \frac{f(t)}{1 - F(t)} = \frac{f(t)}{S(t)}$$

$h(t) \ge 0$ since both $f(t)$ and $S(t)$ are non-negative.

The hazard rate measures the rate at which risk of failure is accumulated. The total risk accumulated up to time t is given by the cumulative hazard function (Cleves, Gould et al. 2008):

$$H(t) = \int_0^t h(u)du$$

$H(t) \geq 0$ since $h(t) \geq 0$.

Given a random failure time T, the mean time to failure μ_T is defined as the area below the survival curve:

$$\mu_T = \int_0^\infty t\, f(t)dt = \int_0^\infty S(t)dt .$$

The median failure $\tilde{\mu}_T$ time is defined to be the 50th percentile of the failure time distribution. In general, survival time data have long, right-tails and the difference between the mean and the median may be considerable. I use the median delays to draw inferences where possible due to the skewed nature of the failure times.

Non-parametric methods make no assumptions about the functional form of the survivor function and the related hazard functions. They are, therefore, commonly used in order to avoid the assumption that some parametric model is correct if there is no valid reason a-priori (Hougaard 2000). A disadvantage of non-parametric analysis is that the effects of covariates are not modelled and the comparison of survival is carried out at a qualitative level across different covariate values (Cleves, Gould et al. 2008).

I use the Kaplan-Meier estimate, also known as product limit estimate of the survivor function $S(t)$ at time t. The Kaplan-Meier estimate assumes independent observation times $T_1, T_2, \ldots T_n$ and corresponding failure indicators $D_1, D_2, \ldots D_n$. For each time point t the risk set is defined by the set of observations whose failure time is greater than or equal to t. The size of the risk set is given by the number of subjects under observation at time t, $R(t) = \sum_i \mathbf{1}\{T_i \geq t\}$, where $\mathbf{1}\{.\}$ is the indicator function. Given the fact that the subject has not failed at the beginning of the interval (t_{j-1}, t_j), the

conditional probability that the subject fails within the interval is $p_j = \Pr(t_{j-1} < T \le t_j \mid t_{j-1} < T)$. The number of failures follows a binomial distribution with probability parameter p_j conditional on the number of non-failed individuals at the beginning of the period. For any subject i at risk at the beginning of the period define a random variable D_{ij} with the binomial distribution:

$$\Pr(D_{ij} = 1) = p_j, \Pr(D_{ij} = 0) = 1 - p_j.$$

The estimate of the conditional probability of failure within the interval is:

$$\hat{p}_j = \frac{\sum_i D_{ij}}{R(t_{j-1})} = \frac{d_j}{n_j}$$

Therefore, the estimate of the survivor function is given by (Kaplan and Meier 1958):

$$\hat{S}(t) = \Pr(T > t) = \prod_{j|t_j \le t} (1 - \hat{p}_j) = \prod_{j|t_j \le t} \left(\frac{n_j - d_j}{n_j} \right)$$

where n_j is the number of subjects at risk, d_j is the number of failures at time t_j and $t_1, t_2, \ldots t_k$ are the observed failure times. The estimate of the survival function is given as the product over all observed failure times (i.e., country-molecule launches) less than or equal to time t. $\hat{S}(t)$ is a right continuous decreasing step function with changes at times of failure. If the largest time value corresponds to a death, $\hat{S}(t)$ becomes eventually 0; otherwise, if the largest time value is censored the function will have a non-zero value at that time point and will be undefined afterward. In mean lifetime calculations, the survival time is assumed to be zero after the largest time to obtain the restricted mean survival estimate, which is a lower bound for the mean survival time. A safer way is the estimation of the median if the observation period is long enough for $\hat{S}(t)$ to cross 0.5. The standard error reported for the Kaplan-Meier estimate $\hat{S}(t)$ is given by Greenwood's formula:

$$Var(\hat{S}(t)) = \hat{S}^2(t) \sum_{j|t_j \le t} \frac{d_j}{n_j (n_j - d_j)}.$$

The reported confidence interval bounds for $\hat{S}(t)$ are calculated as $\hat{S}(t)^{\exp\{\pm z_{\alpha/2}\hat{\sigma}(t)\}}$, where $z_{\alpha/2}$ is the $1-\alpha/2$ quintile of the normal distribution, and $\hat{\sigma}^2(t)$ is the asymptotic variance of $\ln\{-\ln\hat{S}(t)\}$ (Kalbfleisch and Prentice 2002).

$$\hat{\sigma}^2(t) = \frac{\sum_{j|t_j \le t} \frac{d_j}{n_j(n_j - d_j)}}{\left\{\sum_{j|t_j \le t} \ln\left(\frac{n_j - d_j}{d_j}\right)\right\}^2}$$

The real advantage of the non-parametric model is the fit, which can handle any distribution. However, a major disadvantage is that the hazard function is not defined for a discrete distribution and cannot be estimated. The discrete masses of Kaplan-Meier (and the corresponding discrete cumulative hazard estimates of Nelson-Aalen) have to be smoothed by kernel function smoothing to obtain estimates of the hazard function.

Appendix B.3: Semi-parametric Duration Analysis

The standard model for semi-parametric modelling is the Cox model (Cox 1972) according to which the hazard rate for the j'th subject depends on covariates $\mathbf{z_j} = (z_{1j}, z_{2j}, ..., z_{pj})$ and time t as follows:

$$h(t; \mathbf{z}_j) = h_0(t)\exp(\mathbf{z}_j \boldsymbol{\beta}_x)$$

where $\boldsymbol{\beta}$ is a $p \times 1$ vector of unknown parameters to be estimated from the data and $h_0(t)$ is the baseline hazard function for the standard set of conditions $\mathbf{z} = 0$ which describes the dependence of the hazard on time t. $\exp(\mathbf{z}\boldsymbol{\beta})$ is the relative hazard, and $\mathbf{z}\boldsymbol{\beta}$ is the log-relative hazard. In the Cox semi-parametric model the baseline hazard $h_0(t)$ is not parameterized and is left unestimated but the effects of the covariates are parameterized. The flexibility of the Cox model stems from the fact that no assumption is made about the shape of the hazard over time. The shape could be monotonic or non-monotonic but it is restricted to be the same for all subjects, in

other words the subjects' hazards are proportional to each other (Cleves, Gould et al. 2008):

$\frac{h(t;\mathbf{z}_j)}{h(t;\mathbf{z}_m)} = \frac{\exp(\mathbf{z}_j\boldsymbol{\beta}_x)}{\exp(\mathbf{z}_m\boldsymbol{\beta}_x)}$ is constant over time if covariates $\mathbf{z}$ are time-independent.

Exponentiated coefficients in the model give the ratio of the hazards for a one-unit change in the corresponding covariate:

$$\frac{h(t;z_{1j},z_{2j},\ldots,z_{k+1,j},\ldots,z_{pj})}{h(t;z_{1j},z_{2j},\ldots,z_{k,j},\ldots,z_{pj})} = \frac{h_0(t)\exp\left(\sum_{i=1}^{p} z_i\beta_i + \beta_k\right)}{h_0(t)\exp\left(\sum_{i=1}^{p} z_i\beta_i\right)} = \exp(\beta_k)$$

β_k describes the change in the hazard on a logarithmic scale for a change in the corresponding covariate z_k of one unit, while all other covariates are kept fixed. Therefore, $\beta_k > 0$, i.e. $\exp(\beta_k) > 1$ is associated with an increased hazard rate. The Cox PH model provides no estimate of the intercept as it is subsumed into the baseline hazard and handles time-varying covariates by splitting the data at the failure times in the sample. Parameters are estimated using the partial maximum likelihood, which works with likelihood contributions at each failure times, i.e. the conditional probabilities of observing the actual subject experiencing a failure given that there, was a failure at that time instant. Conditional on there being one failure at time T_i, the failure time for subject i, and given the risk set $R(T_i)$, the probability that the failure event belongs to subject i is given by:

$$\Pr(i \text{ fails given the risk set } R(T_i)) = \frac{h_0(T_i)\exp(\mathbf{z}_i\boldsymbol{\beta}_x)}{\sum_{j\in R(T_i)} h_0(T_i)\exp(\mathbf{z}_j\boldsymbol{\beta}_x)}.$$

Only $\boldsymbol{\beta}$ parameters contribute to the probability since baseline hazards cancel. The likelihood is defined as the product over all failure times:

$$L(\boldsymbol{\beta}_x) = \prod_{i:\text{failure times}} \frac{h_0(T_i)\exp(\mathbf{z}_i\boldsymbol{\beta}_x)}{\sum_{j\in R(T_i)} h_0(T_i)\exp(\mathbf{z}_j\boldsymbol{\beta}_x)}.$$

Under the presence of time-varying covariates, the covariates are replaced by their values at the failure times:

$$L(\boldsymbol{\beta}_x) = \prod_{i:\text{failure times}} \frac{h_0(T_i)\exp\{\mathbf{z}_i(T_i)\boldsymbol{\beta}_x\}}{\sum_{j\in R(T_i)} h_0(T_i)\exp\{\mathbf{z}_j(T_i)\boldsymbol{\beta}_x\}}.$$

Likelihood functions defined above are partial likelihoods since no assumptions are made about the baseline hazard at times when there is no failure. Estimates of $\boldsymbol{\beta}$ parameters are obtained by the maximization of the natural logarithm of the partial likelihood function $L(\boldsymbol{\beta}_x)$. Different methods exist to break ties if multiple failures occur at a given failure time (e.g., Breslow, Efron, exact marginal-likelihood method, and the exact partial-likelihood method). I use the Breslow method (1974) to deal with tied failures, which Stata assumes to be the default method (Breslow 1974)[140].

The Cox model removes the effects of time very effectively and is extremely flexible regarding effects of covariates. One disadvantage of the Cox model is that the assumption of proportional hazards is influenced by heterogeneity; similarly for the hazard rate. If the distribution of the effect on the hazard of the neglected covariates follows a positive stable distribution[141], the model still shows proportional hazards, but the regression coefficients are attenuated towards zero (Hougaard 2000).

[140] Breslow method works well when the number of failures in the risk group is small relative to the size of the risk group

[141] Strict stable distributions have the property that, with $Y_1,\ldots,Y_n$ iid random variables, for each n there exists a normalizing constant $c(n)$ such that $D(\sum_{i=1}^{n} Y_i) = D(c(n)Y)$ where $D(Y)$ is the assumed distribution of Y. The constant $c(n)$ takes form $n^{1/\theta}$ with $\theta \in (0,2]$, θ being the characteristic exponent.

APPENDIX C: Appendix to Chapter 3

Appendix C.1: Early Literature of Market Entry and Timing of Launch

The literature on time lags in the availability of pharmaceutical products across different countries started in the late 1960's after the Thalidomide disaster and the resulting 1962 Amendments in the USA (also known as Kefauver Harris Amendment or Drug Efficacy Amendment). These amendments aimed to prevent economic loss by regulating product quality and introduced a requirement for drug manufacturers to provide proof of the effectiveness and safety of all new drugs before approval, and stopped cheap generic drugs being marketed as expensive drugs under new trade names.

The term "drug lag" was coined and popularized by Wardell, a pharmacologist, whose publications increased awareness of the unavailability of new drugs in the US following the 1962 Amendments (Wardell 1973; Wardell 1974; Wardell 1978). Findings of studies by Wardell (1972, 1973, 1978) that analyze the rates and patterns of new drug introductions in the US and Britain during 1962-1971 and 1972-1976 showed that the US lagged behind Britain in terms of drug availability both in terms of time and clinical implications. During 1960-1961 the number of new drug introductions in the US was 1.13 times the British while for 1966-1971 this ratio was only 0.52. The drug lag during 1962-1971 was most marked in cardiovascular, gastrointestinal, respiratory, diuretic and antibacterial drugs (Wardell 1973). Similarly, categories in which the US lagged behind Britain back in 1976 included cardiovascular, peptic ulcer and central nervous system drugs, including therapies for depression, epilepsy, and migraine (Wardell 1978). From an economical point of view, Peltzman (1973) demonstrated that the implication of such delays in the accessibility of new products is a significant welfare loss in the society (Peltzman 1973). Peltzman found that both R&D and the number of new chemical entities entering the market declined following the amendments.

Findings of Wardell were supported by (Grabowski 1980), (Berlin and Jonsson 1986), and (Kaitin 1989). Berlin and Jonsson (1986) compare the licensing times of new drugs during 1960-1982 for Sweden and five other countries (France, West Germany, Italy, Great Britain and USA). On average, NCE[142] licensing dates are considerably later in Sweden, France, Italy and the USA than in West Germany and Great Britain. For NCEs introduced during the period 1960-82, the average time lag (after licensing in the first country) is 2.8 years in the first four countries, compared with 1.6 years in West

[142] New Chemical Entity (NCE) is defined as any new molecular structure, excluding vaccines, diagnostic agents, and new salts, esters and dosage forms of previously approved compounds

Germany and 1.3 years in Great Britain. The delay in all six countries is considerably longer during the period after 1970 than pre-1070 (Berlin and Jonsson 1986). Kaitin and Mattison (1989) show that the US continues to lag behind the UK in the availability of new drugs during 1983-1987 in terms of the length of the lag time (1.9 years for both 1978-1982 and 1983-1987) (Kaitin, Mattison et al. 1989). Some studies suggested that when drug importance and withdrawals are taken into account the US drug lag is not evident or no worse than that of the other countries (de Haen 1975), (Coppinger, Peck et al. 1989).

Cullen (1983) considers the impact of market size, price levels, costs of gaining marketing approval and ease of marketing as influential factors on the diffusion process in terms of mean lags per country and the number of new products launched in each country (Cullen 1983)[143]. Cullen finds that forces that determine launch are different before 1969 and after 1969, which is confirmed later by findings of Parker (1984). While mean lags and the number of drugs launched before 1969 seems to be driven by commercial pull forces, the drugs launched after 1969 do not exhibit predictable diffusion patterns. Cullen explains this by the influence of regulations that changed diffusion from a commercial process to an administered process.

The first attempt by an economist to explain the pattern of pharmaceutical diffusion dates back to 1980. Grabowski studied the diffusion of 169 products launched during 1963-1975 into the UK, USA, France and West Germany, particularly focusing on the period before and after the 1962 Amendments. Grabowski (1980) provides the first regression analysis for the time delay in the literature that investigates the impact of regulatory stringency, market size, therapeutic importance rating of the FDA and national origin of the NCE (which is determined by the location of the R&D lab that made the discovery or the country where the discovering firm is owned). Grabowski shows that the US shifted from leading to lagging behind the UK and Germany in the post-1962 period. The lag with Europe was not confined to drugs with little or modest gain but also included drugs the FDA ranked as significant therapeutic advances. In general drugs with higher sales and higher therapeutic importance (as rated by the FDA) diffused more widely and more rapidly than less important products (Grabowski 1980).

[143] The set of countries considered by Cullen (1983): UK, Colombia, Mexico, Peru, Brazil, Venezuela, Japan, Indonesia, Philippines, Belgium, France, West Germany, Italy, Spain, Austria, New Zealand and the US

This study concludes that the major contributing factor to the lag is the change in regulation.

Parker (1984) investigates the impact of introduction date of the drug (higher international awareness and improved harmonization of registration requirements for new discoveries), regulatory tightness of countries, therapeutic importance, attractiveness of markets (wealth and size of the market) and the type of country (developed vs. developing) on launch delay of drugs across countries by using IMS volume data in 18 countries during 1954-1978. The set of countries considered is divided into rich and poor countries[144],[145]. Arrival time lags are based on first marketing dates, which precludes the identification of delays caused due to regulatory delays (time from submission for MA to clearance) vs. companies actions (time from clearance to marketing). Parker observes a tendency for countries with tight regulatory procedures[146] to acquire drugs earlier than their less stringent counterparts do. In other words, tough regulation in a country does not necessarily imply longer regulatory delays, which contradicts findings from the recent literature. This can be explained by the fact that regulation during the observation period tended to be stricter in wealthier and bigger sized markets, i.e. in markets with a high commercial pull.

Therapeutically more important[147] drugs in Parker's sample tend to have higher sales and achieve wider global coverage (pre-1971) than their less important counterparts. Less developed economies have fewer drugs than their rich counterparts and the mean arrival time lags are larger for the less developed countries. However, after 1970, this pattern changes due to structural differences and redirection of company interests into less developed countries induced by regulation in developed markets. A limitation in this study is the limited availability of sales data; sales in 1976 or 1977 for each drug are used to approximate market attractiveness throughout the observation period. OLS regression of the time lag on the above-mentioned factors is not as methodologically strong as methods used in studies that are more recent.

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[144] Set of rich countries in Parker (1984): Australia, Belgium, France, Italy, Japan, New Zealand, UK, USA and West Germany

[145] Set of poor countries in Parker (1984): Argentina, Brazil, Colombia, Indonesia, Mexico, Peru, Philippines, Spain, Venezuela

[146] Stringency of regulation is determined based on a questionnaire responses obtained from seven companies (absolute and relative regulatory tightness is assessed on a 1 to 5 scale ,where 1 indicates tightest regulatory character)

[147] Therapeutic ratings are determined on a 1 to 5 scale by the Otago University Department of Pharmacology (class 1: fundamental importance, class 5: little or no advance)

Over time, the US drug regulatory policy, highly criticized for causing a drug lag in the US, has served as a model for other countries (Von Grebmer 1980)[148]. Von Grebmer (1980) predicts that the international domino effect will lead to the disappearance of the US drug lag back in the 60's. Similarly, de Haen (1975) predicts that the European and the US "drug lag" will be closed. The literature suggests that throughout 1990s Europe has had more regulation in the post-marketing phase in terms of price controls, which has reversed the balance of lags between the US and the EU over the past decade.

All of the researchers who conducted multi-country drug lag studies applied several criteria to identify significant or important NCEs. The most common approach was to define a set of consensus NCEs-about 25% of the total that were introduced in the majority of the countries studied (Coppinger, Peck et al. 1989). Barrel (1985) finds that there is a direct relationship between the therapeutic contribution of a new drug and its likelihood of achieving widespread introductions (Barral 1985). Parker (1984) reports a similar observation. If this finding is correct, most of one-market NCEs do not simply disperse among countries more slowly than others do: they are never going to be widely available due to their marginal therapeutic advantages.

Hass et al. (1984) study the survival of the NCEs in the US and the UK markets. For each year that NCEs were introduced in the US or UK during 1960-1982, Hass et al. identified those NCEs that were no longer marketed at the end of 1982 and produced a net measure of availability for the NCEs originally introduced in any given year (Hass, Portale et al. 1984). Substantially different discontinuation rates are observed depending on whether the NCE was mutually available or available exclusively in one market. Mutually available NCEs had a discontinuation rate of 1%, whereas exclusively available NCEs had a discontinuation rate of 14% in the US and 35% in the UK, most of the terminations being motivated by economic considerations and due to disappointing therapeutic contributions. This finding shows the importance of considering therapeutic benefits in the analysis of drug approval rates in addition to the number of approvals.

[148] Pre-market drug regulation and approval came into Europe after 1962 with the thalidomide experience whereas regulatory controls in the US began around 1938 with the passage of the Food, Drug and Cosmetic Act. In 1962 Kefauver Harris Amendments extended FDA controls by requiring that companies prove safety and efficacy and demonstrate effectiveness through controlled clinical investigations, which was the main source for longer and costlier development periods for new drugs post-1962. Neither of countries other than the US required the IND (investigational new drug) procedure for clinical testing at that time

Coppinger, Peck et al. (1989) find evidence that 1984 might have been the pivotal year in the history of drug introduction patterns between the US and the UK. After 1984, the drug lag for US no longer seems to persist; however, this is a tentative result as the study cautions that it might be placing too much weight on the numeric count of recent introductions from 1984-1987 compared to the period 1962-1983 (Coppinger, Peck et al. 1989). Kaitin compares the introduction of all new drugs approved in the US and the UK during Jan 1977- Dec 1987 and observes no change in the US lag time vis-à-vis UK during 1983-1987 (Kaitin, Mattison et al. 1989). Similarly, Kaitin concludes that there are small differences in discontinuations, which does not support the argument that delay protects the public from serious unforeseen adverse effects. Schweitzer, Schweitzer et al. (1996) compare the approval dates of 34 important pharmaceuticals that were approved in the US during 1970-1988 with the other G7 countries and Switzerland. Contrary to earlier findings this study finds that the US was relatively fast in approving drugs and that it does not suffer from a substantial drug lag (Schweitzer, Schweitzer et al. 1996).

One of the older studies by LaFrancis Popper et al (1994) tests the relationship among the types of regulation, product introductions and the timing of entry into the largest markets (US, Japan, West Germany, France, Italy, UK, Spain, and Canada) during 1970 - 1989. The type of regulation is found to have a bigger impact on timing than the number of products launched. National formularies appear to have little relationship with product introductions or timing. Both generic substitution and national health plans slow product introductions. Compulsory out-licensing[149] significantly increases the time to reach the market. Acceptance of non-domestic clinical testing is associated with a shorter time to market (LaFrancis Popper and Nason 1994).

Andersson (1992) reviews studies primarily related to the delay in introduction of new drugs and studies primarily related to the number of introduced new drugs. Most studies have found the US, Sweden, and Norway to have a long delay in the introduction of new drugs. The UK and (West) Germany in general have the shortest delays. There are also large differences in the number of introduced new drugs. In most studies, the US and Norway have introduced far fewer new drugs than any other industrialized country. In general (West) Germany, France, the UK, and Italy have introduced the largest

[149] Companies can apply for a licence to manufacture, without the authorisation of the patent holder, pharmaceutical products for export to countries in need of medicines and facing public health problems

number of new drugs. Regulatory processing time and regulatory stringency are associated with delays in introduction (Andersson 1992).

The impact of the stringency of the drug regulatory systems emerges as an important determinant of the drug lag in the early literature. However, the introduction of the UK Medicines Act in 1971 along with subsequent efforts of the FDA to speed the review process in the late 1970s and early 80s helped close the long-discussed gap between the US and the UK drug introductions. Economical factors, demand for particular drugs, differences in medical practice and culture became other important considerations for pharmaceutical firms during this period.

Impact of Drug Review Times

As described in Chapter 2, there are a couple of regulatory hurdles firms need to overcome before commercializing a new drug product. Once the firm has carried out the pre-clinical and clinical trials necessary to demonstrate safety and efficacy (the first hurdle), the manufacturer submits the drug for market authorization. The review of the new product dossier by the regulatory authority (FDA[150], EMEA[151] or any national authority) and approval of marketing authorization (MA) has been termed as the second-hurdle. Chapter 2 provided descriptive evidence by using Kaplan-Meier estimates on how the stringency of marketing authorization affects the timing and availability of pharmaceutical product launches.

Several empirical studies in the literature have compared drug review times across different periods or countries as a determinant of differentials in launch delays. The pioneering work belongs to Dranove and Meltzer (1994) who model a Weibull parameterization of time-to-approval from the first worldwide patent application (discovery date) to new drug approval as a proxy of market entry or access to the drug in the US. The study uses US patent registers to collect the data for analysis. Explanatory variables used in the Weibull model are marketing importance of the drug (US sales volume and the number of countries the drug launched in), scientific importance (citations in medical textbooks, citations in medical journals[152] and subsequent patent applications, and FDA ranking of therapeutic novelty), drug characteristics (whether it is indicated for old or young people, and whether it is for

[150] Food and Drug Administration

[151] European Medicines Agency

[152] total number of articles indexed between 1962-1990 for each NME

chronic vs. acute use) and firm characteristics (cumulative number of FDA approvals before the approval of the drug). This study confirms that more important drugs are developed and approved more rapidly. Within the US setting, this also translates to quicker launch since products do not have to go through pricing negotiations as in the EU. Importance is found to affect both the time from first worldwide patent application to new drug application (NDA) and time from NDA to NDA approval. Generally, quicker approval is observed if the firm is domestic which is confirmed by more recent studies that investigate launch in other markets, particularly in Europe. However, the generalizability of the results to the EU context is limited due to the different dynamics in the EU (Dranove and Meltzer 1994).

Several studies from the US have identified that firm attributes may have an effect on the review times, often favouring larger firms in terms of faster FDA approval times. Carpenter and Turenne (2004) analyze 766 new molecular entities submitted to the FDA from 1979 to 2000. Their findings suggest that large-firm advantage in pharmaceutical regulation is primarily due to two factors: (1) enhanced regulator familiarity with large firms (2) regulatory favour for "early entrants" to a disease market, induced from disease-specific consumer pressure for approvals. The analysis concludes that as much as 70% of observed large-firm advantage in expected FDA approval times can be attributed to these factors, and 30-55% to familiarity alone (Carpenter and Turenne 2004). Such evidence is lacking for the European context; however, it is likely that familiarity of the European regulators with large firms has also positively affected approval times for these firms.

The US witnessed a number of legislative acts passed in the 1980s and 1990s designed to encourage the development of innovative products, especially for rare, serious or life-threatening diseases, and to ensure that patients had timely access to these treatments. The Tufts Centre for the Study of Drug Development analysed clinical development and approval data for 554 therapeutics approved in the US from 1980–2001 to assess the impact of these modifications. Trends in the number of approved products and the clinical development and approval times indicated that the effects of these changes were generally beneficial during mid- to late-1990s, but that the gains have not been sustained in the early 2000s (Reichert 2003).

Thomas, McAuslaine et al. 1998 analyze data on review times for compounds approved between 1990 and 1995 in at least one of nine major pharmaceutical markets (Australia,

Canada, France, Germany, Italy, Japan, Spain, the UK, and the US). Review times are shown to be decreasing in the majority of the markets. In 1995 the average review time was around two years in most countries. The study indicates that there are differences in the time a compound spends in review between authorities, even when the same compound is submitted in the same time frame (Thomas, McAuslaine et al. 1998). The differences could be attributed to the quality of the dossier submitted, company response time to questions raised during the review, and the ability of authorities to manage the review both effectively and efficiently. A later study by Carpenter, Chernew et al. (2003) suggest that some of the differentials could be due to staffing patterns and the capacities of the regulatory authorities (Carpenter, Chernew et al. 2003). NDA review times shortened by 3.3 months for every 100 additional FDA staff during 1977-2000. In particular, the amount of funding available for the review stuff is found to have an important influence on NDA review times[153].

In the European setting, the review process has been harmonized for certain disease areas since 1995 with the establishment of the centralized approval procedure. Under the centralized procedure, companies submit a single marketing authorization application to the European Medicines Agency and obtain the right to commercialize their product in all EU member states (plus Iceland, Liechtenstein and Norway). To enhance the quality and speed of drug development for products that go through the EMEA's centralized procedure, the European Commission has passed additional regulations such as exceptional circumstances approvals and orphan designations.

[153] Prescription Drug User Fee Act (PDUFA) of 1992,augmented the FDA's budget through the charging of user fees

Appendix C.2: Discrete Time Survival Analysis

Discrete-time survival analysis is concerned with the analysis of time-to-event data whenever survival times are intrinsically discrete or grouped into discrete intervals of time (interval censoring). Discrete-time survival methods can be fitted with the maximum likelihood method. Logit for the discrete-time logistic hazard model or cloglog for the discrete-time proportional hazards model can be used.

Estimation is applied to a specially organized dataset and the sample likelihood is written in a form identical to the likelihood of a binary dependent variable multiple regression model. The dataset is organized such that there is one observation for each period when the subject is at risk of experiencing the transition event. This is established by expanding the dataset with the "expand" command in Stata. Censoring variables are defined as in the Cox model (censoring variable is one if the failure occurs and zero otherwise). In addition, indicator variables (d_{it}) are defined such that the indicator variable is equal to one only if t equals the failure time and the subject is not censored; for all other periods, the indicator variable is zero.

Different from the Cox model, cloglog requires the definition of additional covariates to describe the pattern of duration dependence. Common examples for duration dependence specification include:

1) p-th order polynomial function of time, i.e. $\gamma_1 t + \gamma_2 t^2 + \gamma_3 t^3 + ... + \gamma_p t^p$, where γ_i's are shape parameters. With a quadratic specification t and t^2 are added as variables; the interval hazard is U-shaped or inverse-U shaped (and hence non-monotonous duration dependence can be estimated). A cloglog specification with a quadratic specification is $\text{cloglog}\left\{h\left(t, \mathbf{z}_j\right)\right\} = \gamma_1 t + \gamma_2 t^2 + \mathbf{z}_j \boldsymbol{\beta}_x$, and γ_i's are estimated together with $\boldsymbol{\beta}_x$.

2) Piecewise constant such that groups of months have the same hazard rate with different hazards between groups. A piecewise constant specification can be defined by defining a set of dummy variables, with each group of periods sharing the same hazard rate. A semi-parametric model analogous to the Cox regression model can be defined using separate dummy variables for each duration interval.

3) Discrete-time analogue to the continuous Weibull model can be obtained by $\alpha \ln(t)$. The shape of the hazard monotonically increases if $\alpha > 0$, decreases if $\alpha < 0$ or is constant if $\alpha = 0$ (Jenkins 2005).

If no duration variable is assigned, a model with a constant hazard rate is fitted. Discrete-time survival analysis is then fit by a binary dependent variable multiple regression model with d_{it} as the dependent variable[154]. The cloglog command with d_{it} as the dependent variable in Stata fits the probability of failure at t conditional on the covariates and the fact that failure prior to t has not occurred (i.e. the interval hazard rate is estimated as):

$$\Pr(d_{jk}(t) = 1 \mid T_{jk} \geq t) = h(t, \mathbf{z}_j) = 1 - \exp(-\exp(\mathbf{z}_j \boldsymbol{\beta}_x + \gamma_t)),$$

where γ_t is a function of t that describes the duration dependence and T_j is the failure time of subject j. For example, for a quadratic specification the hazard is $h(t, \mathbf{z}_j) = 1 - \exp(-\exp(\gamma_1 t + \gamma_2 t^2 + \mathbf{z}_j \boldsymbol{\beta}_x))$.

The marginal effect is given by:

$$\frac{\partial h}{\partial z_j} = \exp\left\{-\exp\left(\mathbf{z}_j \boldsymbol{\beta} + \gamma_t\right)\right\} \exp\left(\mathbf{z}_j \boldsymbol{\beta} + \gamma_t\right) \beta_j,$$

which implies that the marginal effect has the same sign as the estimated parameter.

Clustering can be used in Stata to relax the independence assumption required by the complimentary log-log estimator. Clustering would assume independence between the clusters instead of individual observations. With cloglog, the transformation is not symmetric. Typically, cloglog is used when the negative or positive outcome is rare (in this chapter the rare event corresponds to the launch event). The log-likelihood function for cloglog with a quadratic specification is:

$$\ln L = \sum_{j \in S} w_j \ln F(\gamma_1 t + \gamma_2 t^2 + \mathbf{z}_j \boldsymbol{\beta}) + \sum_{j \notin S} w_j \ln\left\{1 - F(\gamma_1 t + \gamma_2 t^2 + \mathbf{z}_j \boldsymbol{\beta})\right\}$$

where S is the set of all observations j such that d_{jt}=1, $F(z) = 1 - \exp(-\exp(z))$ and w_j denotes the optional weights ($\mathbf{z}_j$ may include duration dependence terms).

[154] Stata Reference Manual, Volume 1, 2009, page 21.

Interpretation of Cox and Cloglog Estimates

Both cloglog and Cox provide the same estimates of $\boldsymbol{\beta}$ [or $\exp(\boldsymbol{\beta})$] for regulation, competition, molecule and firm characteristics in the launch hazard equations. Note that both for the Cox and Cloglog model, the marginal effect $\partial h / \partial z_i$ has the same sign as the estimated parameter β_i since $h_0(t) \geq 0$ and $\exp(.) > 0$.

Table C.1 Comparison of cloglog and Cox models

Function	*Cloglog*	*Cox*
Hazard Rate: h	$1-\exp(-\exp(\mathbf{z}\boldsymbol{\beta}+\gamma_t))$	$h_0(t)\exp\{\mathbf{z}\boldsymbol{\beta}\}$
Marginal Effect: $\partial h / \partial z_i$	$\exp\{-\exp(\mathbf{z}\boldsymbol{\beta}+\gamma_t)\}\exp(\mathbf{z}\boldsymbol{\beta}+\gamma_t)\beta_i$	$h_0(t)\exp\{\mathbf{z}\boldsymbol{\beta}\}\beta_i$
$\exp(\beta_i)$	$\frac{\ln(h'-1)}{\ln(h-1)}$	$\frac{h'}{h}$

Note: h' is the new hazard rate when z_i increases by 1

Stata reports parameter estimates either in the exponentiated form $\exp(\beta_i)$ or non-exponentiated form as β_i. In the Cox model, $\exp(\beta_i)$ has an intuitive interpretation. If z_i increases by 1, the hazard becomes $h'(t) = h_0(t)\exp\{\mathbf{z}(t)\boldsymbol{\beta}\}\exp(\beta_i) = h(t)\exp(\beta_i)$. $\exp(\beta_i)$ in the Cox model, therefore, shows by how much the hazard increases when the covariate z_i is changed by 1 unit. The same interpretation, however, is not valid under the cloglog model (see Table A.2.1). With $\exp(\beta_i)>1$ for cloglog this implies that $\ln(h'-1) > \ln(h-1)$, i.e. $h' > h$ but the effect is not multiplicative. Both in the Cox and the Cloglog models if $\exp(\beta_i) \geq 1$ $(\beta_i \geq 0)$, then an increase in z_i increases h. On the other hand, if $\exp(\beta_i) < 1$ $(\beta_i < 0)$, an increase in z_i decreases h.

Another commonly used approach for discrete hazard estimation is the logistic model. For short intervals, the logistic model becomes very similar to the discrete proportional hazards model. The logistic model is discussed in Appendix D.

Appendix C.3: Data Analysis

C.3.1 Descriptive Statistics

Table C.2 Descriptive Statistics for Variables used in Regressions

External Environment		Descriptive Statistics			
Regulatory Environment	*Description*	*Mean*	*Std Dev*	*Min*	*Max*
Expected Price ($/SU)	Avg Non-Generic Price/SU in Ctry-ATC4	42.87	174.92	0	3509.06
Relative Price	High Price EU	0.29	0.46	0	1
Price Setting	External Referencing	0.83	0.37	0	1
Market Environment					
Expected Market Size (000 SUs)	Total SU in Ctry-ATC4	24,736	96,220	0.001	2,413,040
GDP per capita ($)	GDP per capita ($)	26,804	8,080	8,046	46,336
Population (000)	Population (000s)	41,359	51,691	5,165	303,598
Age profile of the population	% Population > 65 yrs	15.31	3.36	5.32	22.11
Health profile of the population	Life expectancy in yrs	78.61	2.73	69.5	82.8
Corruption	Corruption Perception Index	7.06	1.93	3.1	10
Competitive Environment					
Market Concentration	Molecule Concentration in Ctry-ATC4(IHH)	55239.77	173633.80	304.76	8396584
Intermolecular Competition	Number of Molecules in Ctry-ATC4	9.89	15.94	0	226
Generic Competition	Numb. of Molecs with Generic Comp in Ctry-ATC4	7.85	16.25	0.01	198
Internal Environment					
Firm Characteristics					
Economies of Scope	Firm Sales (global) in 2007	14,100,000	12,900,000	0	37,800,000
	Number of Countries Firm has Launched in	15.71	7.05	1	20
Economies of Scale	Firm's Total Number of Molecules	453.51	401.01	1	1365
	Local Firm Experience (number of molecs launched)	112.14	121.50	1	769
Location of Firm Headquarters	Domestic Launch	0.11	0.31	0	1
Molecule/Product Characteristics					
Therapeutic/Commercial Importance	Global Molecule Sales in 2007	357,758	766,566	0	11,500,000
	Molecule's Global Reach (total markets launched in)	15.40	3.09	10	20
Cumulative Markets Diffused at t	Markets Launched in at t	3.82	5.77	0	20
Period of Launch (old vs. new molec.)	First Launch Before 1999	0.67	0.47	0	1

Note: all lags are by one quarter

Number of Molecule Launches by Country

The number of molecules launched in each country varies considerably with respect to the market. Germany is the market with the highest number of molecules in total and the highest number of molecules that launched most recently. Sweden, Portugal, Finland, Netherlands exhibit a relatively low number of molecule launches. However, in some countries with high numbers of molecule launches, molecules can be potentially local without any commercial/therapeutic importance on a global scale (e.g. in Japan). The average number of countries a molecule launches is 7.9 (with a standard deviation of 6.6); ignoring one-market molecules, the average number of markets a molecule reaches is 9.8 with a standard deviation of 6.3. About half of the molecules launched in less than 6 markets and about 21% of the molecules launched in one market only.

Table C.3 Number of Molecules Launched by Country

All Molecules	
SWEDEN	987
FINLAND	1173
NETHERLANDS	1343
PORTUGAL	1374
GREECE	1514
TURKEY	1665
BELGIUM	1675
CANADA	1749
SPAIN	1814
UK	1817
AUSTRIA	1829
SAFRICA	1885
JAPAN	1982
POLAND	2012
AUSTRALIA	2050
ITALY	2133
US	2138
SWITZERLAND	2242
FRANCE	2306
GERMANY	2662

Molecules that Launched during 1999-2008	
PORTUGAL	505
SWEDEN	587
FINLAND	642
NETHERLANDS	727
SPAIN	769
BELGIUM	784
GREECE	999
AUSTRIA	1029
ITALY	1089
JAPAN	1145
CANADA	1149
SWITZERLAND	1158
TURKEY	1187
UK	1233
SAFRICA	1299
POLAND	1452
AUSTRALIA	1531
FRANCE	1563
US	1636
GERMANY	1913

Table C.4 Mean Number of Corporations by Country (Brand and Generic Status)

Country	*Mean Number of Corporations*	*License/ Original Brand*	*Unbranded*	*Generic*	*Non-generic*
Australia	5.2	1.5	7.55	6.86	4.09
Austria	2.99	1.97	3.73	5.8	3.16
Belgium	2.68	2.01	2.79	5.74	3.74
Canada	4.05	1.58	6.51	8.35	3.36
Finland	2.31	2.09	4.53	4.95	2.34
France	4	1.79	8.43	10.56	5.78
Germany	10.88	8.99	11.89	19.22	11
Greece	3.18	1.54	1.91	15.17	1.95
Italy	4.31	2.4	10.92	16.41	4.54
Japan	7.37	1.94	9.29	17.42	10.7
Netherlands	5.17	7.86	8.47	9.95	7.83
Poland	3.77	2.15	5.61	7.67	3.43
Portugal	3.26	1.74	14	13.33	4.12
South Africa	3.62	1.61	4.03	7.87	3.97
Spain	4.06	2.49	12.96	13.2	7.38
Sweden	2.44	3.32	4.3	4.88	3.31
Switzerland	3.87	1.66	3.47	6.15	5.11
Turkey	4.08	1.62	8.91	7.4	3.8
UK	4.42	1.7	9.48	12.31	3.89
US	9.5	1.72	24.11	40.44	10.45

Table C.5 Average Molecule Prices (prices per SU in $s)

Country	*License / Original Brands*	*Other Brands*	*Unbranded*	*Generic*	*Non-Generic*
Australia	0.47	0.11	0.136	0.124	0.342
Austria	0.575	0.161	0.327	0.221	0.497
Belgium	0.489	0.175	0.191	0.172	0.384
Canada	0.959	0.122	0.143	0.15	0.769
Finland	0.798	0.177	0.217	0.172	0.575
France	0.683	0.101	0.202	0.167	0.436
Germany	0.759	0.182	0.16	0.164	0.632
Greece	0.434	0.167	0.07	0.135	0.387
Italy	0.598	0.204	0.249	0.188	0.484
Japan	0.534	0.141	0.195	0.088	0.339
Netherlands	0.973	0.229	0.16	0.158	0.764
Poland	0.303	0.106	0.05	0.106	0.216
Portugal	0.351	0.144	0.343	0.241	0.272
South Africa	0.23	0.061	0.032	0.046	0.11
Spain	0.345	0.134	0.128	0.114	0.284
Sweden	0.795	0.136	0.108	0.113	0.558
Switzerland	0.873	0.171	0.283	0.255	0.583
Turkey	0.102	0.043	0.044	0.05	0.082
UK	0.607	0.112	0.115	0.126	0.5
US	2.173	0.314	0.144	0.171	1.896

Table C.5 shows the average molecule prices in individual countries with respect to branded versus generic categories. Prices are, however, not directly comparable as mix of dosage, form and strength for products are different across countries.

C.3.2 Regression Results

Table C. 6 Marginal Effects for Cloglog and Cox Estimates (Molecules with First Launch after 1993)

Molecules with global launch post 1993	*Marginal Effects in Cox Regressions*				*Marginal Effects in Cloglog (quadratic in t)*				*Marginal Effects in Cloglog (semi-parametric)*			
	1	2	3	4	1	2	3	4	1	2	3	4
Log Lagged Avg Non-Generic Price/SU in Ctry-ATC4	0.160*** [0.03]	0.001 [0.0007]	0.003 [0.08]	0.198*** [0.05]	0.004*** [0.0006]	0.003*** [0.0006]	0.003*** [0.0006]	0.003*** [0.0006]	0.004*** [0.0006]	0.003*** [0.0006]	0.003*** [0.0006]	0.003*** [0.0006]
Log Lagged Total SU in Ctry-ATC4	0.092*** [0.02]	0 [0.0005]	0.003 [0.06]	0.147*** [0.04]	0.002*** [0.0004]	0.002*** [0.0004]	0.002*** [0.0004]	0.002*** [0.0004]	0.002*** [0.0004]	0.002*** [0.0004]	0.003*** [0.0004]	0.002*** [0.0004]
Log Population (000s)		0 [0.0005]	-0.095 [2.15]			-0.001 [0.00]	-0.13 [0.08]			-0.002 [0.00]	-0.109 [0.08]	
Population > 65 yrs		0 [0.0004]	0 [0.01]			0.003*** [0.0005]	0 [0.0024]			0.003*** [0.0005]	0 [0.0023]	
Life expectancy in yrs		-0.002 [0.00]	0.003 [0.07]			-0.010*** [0.0010]	0.003 [0.003]			-0.010*** [0.0010]	0.003 [0.003]	
Log GDP per capita ($)		0.008 [0.01]	0.051 [1.20]			0.052*** [0.01]	0.047* [0.02]			0.052*** [0.01]	0.052* [0.02]	
Corruption Perception Index		0.001 [0.00]	0.003 [0.07]			0.003*** [0.0008]	0.003 [0.0028]			0.003*** [0.0009]	0.003 [0.0025]	
Years since global launch (t)					0 [0.0010]	0.002 [0.0011]	0.003** [0.0011]	0.004*** [0.0011]				
Years since global launch squared (t^2)					-0.000** [0.0001]	-0.000*** [0.0001]	-0.001*** [0.0001]	-0.001*** [0.0001]				
Country Dummies	No	No	Yes	Yes	No	No	Yes	Yes	No	No	Yes	Yes

ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calendar Year Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Number of Observations	58530	54794	54794	58530	58530	54794	54794	58530	58530	54794	54794	58530
LogLikelihood	-16860	-15848	-15790	-16682	-10727	-10058	-10001	-10541	-10762	-10089	-10028	-10572
Akaike's Info Criteria	33765	31751	31671	33449	21506	20179	20100	21171	21573	20236	20150	21229
Bayesian Info Criteria	33972	32001	32081	33826	21740	20455	20537	21575	21788	20495	20569	21616

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets). Non-exponentiated parameter estimates reported . Models (2) and (3) have fewer observations because data to control for country characteristics is not available for South Africa in the OECD database

C.3.2.1 Multicollinearity

Table C.7 VIF estimates for Model 1

	Parametric	
	Model 1	
Variable	VIF	1/VIF
t^2	9.16	0.109226
t^2	9.06	0.110355
L3_ln_pr_SU_atc4Ctry_	2.27	0.440197
ATC1 == L	2.19	0.455908
ATC1 == N	2.14	0.467087
ATC1 == J	2.03	0.491872
L3_ln_SU_atc4Ctry_	1.93	0.517876
year == 2000	1.60	0.624328
ATC1 == M	1.60	0.625011
year == 2001	1.59	0.628895
ATC1 == S	1.56	0.642352
year == 2002	1.56	0.642789
ATC1 == B	1.54	0.648456
year == 2003	1.53	0.652056
ATC1 == G	1.51	0.663724
year == 2004	1.48	0.676272
ATC1 == C	1.45	0.691575
year == 2005	1.43	0.697903
year == 2006	1.37	0.72777
ATC1 == H	1.29	0.772777
ATC1 == R	1.27	0.787184
ATC1 == D	1.25	0.799051
year == 2007	1.21	0.824842
ATC1 == V	1.15	0.866365
year == 2008	1.08	0.928658
Mean VIF	**2.17**	

	Semi-Parametric	
	Model 1	
Variable	VIF	1/VIF
ATC1 == L	2.19	0.456797
L3_ln_pr_SU_atc4Ctry_	2.18	0.457802
ATC1 == N	2.12	0.472167
ATC1 == J	2.02	0.494289
L3_ln_SU_atc4Ctry_	1.91	0.524011
year == 2000	1.6	0.62633
ATC1 == M	1.59	0.627956
year == 2001	1.58	0.631202
year == 2002	1.55	0.647097
ATC1 == S	1.54	0.650973
ATC1 == B	1.52	0.658891
year == 2003	1.52	0.659233
ATC1 == G	1.51	0.663748
year == 2004	1.45	0.689106
ATC1 == C	1.45	0.69197
year == 2005	1.39	0.720139
year == 2006	1.33	0.752184
ATC1 == H	1.28	0.781191
ATC1 == R	1.27	0.78811
ATC1 == D	1.24	0.804415
year == 2007	1.17	0.853225
ATC1 == V	1.15	0.869405
year == 2008	1.04	0.959398
Mean VIF	**1.55**	

Commands

```
xi: regress _d  L3_ln_pr_SU_atc4Ctry_ L3_ln_SU_atc4Ctry_  i.year i.atc1  _t _t2
estat vif
```

Table C.8 VIF estimates for Model 2

	Parametric	
	Model 2	
Variable	VIF	1/VIF
LifeExp_	10.78	0.0927
ln_GDPcap_	10.38	0.0963
t	9.44	0.1059
t^2	9.44	0.1059
pcntover65_	4.61	0.2168
CPI_	4.25	0.2351
L3_ln_pr_SU_atc4Ctry_	2.87	0.3486
L3_ln_SU_atc4Ctry_	2.83	0.3533
ATC1 == L	2.2	0.4539
ATC1 == N	2.14	0.4683
ATC1 == J	2.02	0.4950
year == 2000	1.61	0.6203
year == 2001	1.61	0.6203
ln_popn_	1.61	0.6230
year == 2002	1.6	0.6249
year == 2004	1.59	0.6272
year == 2003	1.59	0.6296
ATC1 == M	1.58	0.6328
ATC1 == B	1.56	0.6408
_Iyear_2005	1.54	0.6474
ATC1 == S	1.53	0.6515
year == 2006	1.51	0.6604
ATC1 == G	1.49	0.6694
ATC1 == C	1.44	0.6952
year == 2007	1.32	0.7594
ATC1 == H	1.31	0.7621
ATC1 == R	1.27	0.7870
ATC1 == D	1.25	0.8012
ATC1 == V	1.17	0.8553
year == 2008	1.1	0.9099
Mean VIF	2.96	

	Semi-Parametric	
	Model 2	
Variable	VIF	1/VIF
LifeExp_	10.66	0.0938
ln_GDPcap_	10.32	0.0969
pcntover65_	4.58	0.2184
CPI_	4.24	0.2361
L3_ln_pr_SU_atc4Ctry_	2.78	0.3593
L3_ln_SU_atc4Ctry_	2.75	0.3639
ATC1 == L	2.2	0.4543
ATC1 == N	2.11	0.4729
ATC1 == J	2.01	0.4987
year == 2000	1.61	0.6220
year == 2001	1.61	0.6222
year == 2002	1.59	0.6290
ATC1 == M	1.58	0.6343
ln_popn_	1.57	0.6358
year == 2003	1.57	0.6363
year == 2004	1.57	0.6385
ATC1 == B	1.54	0.6500
ATC1 == S	1.52	0.6582
year == 2005	1.5	0.6670
ATC1 == G	1.49	0.6697
year == 2006	1.47	0.6799
ATC1 == C	1.44	0.6954
ATC1 == H	1.3	0.7698
year == 2007	1.28	0.7824
ATC1 == R	1.27	0.7885
ATC1 == D	1.24	0.8052
ATC1 == V	1.16	0.8594
year == 2008	1.07	0.9345
Mean VIF	2.46	

Commands:

xi: regress _d L3_ln_pr_SU_atc4Ctry_ L3_ln_SU_atc4Ctry_ ln_popn_ pcntover65_ LifeExp_ ln_GDPcap_ CPI_ i.year i.atc1 _t _t2

estat vif

Table C.9 VIF estimates for Model 3

	Parametric	
	Model 3	
Variable	VIF	1/VIF
ln_popn_	13339.51	0.0001
country ==JAPAN	3942.07	0.0003
country ==US	2164.04	0.0005
country ==TURKEY	1795.79	0.0006
country ==ITALY	1112.16	0.0009
country ==FRANCE	1035.24	0.0010
country ==GERMANY	980.36	0.0010
country ==FINLAND	965.77	0.0010
country ==UK	586.20	0.0017
country ==POLAND	583.51	0.0017
country ==SWITZERLAND	549.94	0.0018
country ==AUSTRIA	364.50	0.0027
country ==SPAIN	337.94	0.0030
LifeExp_	288.25	0.0035
country ==GREECE	237.72	0.0042
country ==BELGIUM	222.96	0.0045
country ==PORTUGAL	207.08	0.0048
country ==SWEDEN	194.69	0.0051
ln_GDPcap_	165.23	0.0061
country ==CANADA	142.29	0.0070
pcntover65_	136.44	0.0073
CPI_	38.20	0.0262
year == 2006	20.77	0.0482
year == 2005	17.16	0.0583
year == 2004	15.51	0.0645
year == 2007	14.41	0.0694
country ==NETHERLANDS	13.86	0.0721
year == 2003	9.90	0.1010
t	9.70	0.1030
t^2	9.58	0.1044
year == 2002	7.88	0.1269
year == 2001	5.53	0.1808
year == 2008	4.60	0.2173
year == 2000	3.03	0.3299
L3_ln_pr_SU_atc4Ctry_	3.00	0.3330
L3_ln_SU_atc4Ctry_	2.94	0.3400
ATC1 == L	2.24	0.4470

	Semi-Parametric	
	Model 3	
Variable	VIF	1/VIF
ln_popn_	13305.64	0.0001
country ==JAPAN	3934.02	0.0003
country ==US	2158.56	0.0005
country ==TURKEY	1793.1	0.0006
country ==ITALY	1109.92	0.0009
country ==FRANCE	1032.99	0.0010
country ==GERMANY	977.98	0.0010
country ==FINLAND	963.34	0.0010
country ==UK	584.68	0.0017
country ==POLAND	583.02	0.0017
country ==SWITZERLAND	548.57	0.0018
country ==AUSTRIA	363.65	0.0028
country ==SPAIN	337.23	0.0030
LifeExp_	288.22	0.0035
country ==GREECE	236.91	0.0042
country ==BELGIUM	222.27	0.0045
country ==PORTUGAL	206.33	0.0048
country ==SWEDEN	194.17	0.0052
ln_GDPcap_	165.07	0.0061
country ==CANADA	141.9	0.0070
pcntover65_	136.18	0.0073
CPI_	38.17	0.0262
year == 2006	20.69	0.0483
year == 2005	17.1	0.0585
year == 2004	15.47	0.0646
year == 2007	14.35	0.0697
country ==NETHERLANDS	13.85	0.0722
year == 2003	9.88	0.1012
year == 2002	7.87	0.1271
year == 2001	5.53	0.1809
year == 2008	4.57	0.2190
year == 2000	3.03	0.3300
L3_ln_pr_SU_atc4Ctry_	2.87	0.3481
L3_ln_SU_atc4Ctry_	2.85	0.3503
ATC1 == L	2.23	0.4476
ATC1 == N	2.13	0.4692
ATC1 == J	2.03	0.4921

ATC1 == N	2.15	0.4647
ATC1 == J	2.05	0.4886
ATC1 == M	1.59	0.6302
ATC1 == B	1.58	0.6328
ATC1 == S	1.55	0.6463
ATC1 == G	1.50	0.6661
ATC1 == C	1.45	0.6900
ATC1 == H	1.32	0.7557
ATC1 == R	1.28	0.7802
ATC1 == D	1.26	0.7947
ATC1 == V	1.17	0.8516
Mean VIF	615.56	

ATC1 == M	1.58	0.6315
ATC1 == B	1.56	0.6429
ATC1 == S	1.53	0.6537
ATC1 == G	1.5	0.6665
ATC1 == C	1.45	0.6901
ATC1 == H	1.31	0.7629
ATC1 == R	1.28	0.7820
ATC1 == D	1.25	0.7987
ATC1 == V	1.17	0.8553
Mean VIF	640.41	

Commands: xi: regress _d L3_ln_pr_SU_atc4Ctry_ L3_ln_SU_atc4Ctry_ ln_popn_ pcntover65_ LifeExp_ ln_GDPcap_ CPI_ i.year i.atc1 i.countrynosector _t _t2

estat vif

Table C.10 VIF estimates for Model 4

	Parametric	
	Model 4	
Variable	VIF	1/VIF
t	9.54	0.1049
t^2	9.43	0.1061
L3_ln_pr_SU_atc4Ctry_	3.05	0.3282
L3_ln_SU_atc4Ctry_	2.99	0.3339
country ==JAPAN	2.26	0.4429
ATC1 == L	2.23	0.4483
country ==TURKEY	2.17	0.4602
ATC1 == N	2.16	0.4637
country ==POLAND	2.06	0.4847
ATC1 == J	2.06	0.4852
country ==SAFRICA	1.95	0.5128
country ==ITALY	1.87	0.5346
country ==FRANCE	1.85	0.5394
country ==GREECE	1.84	0.5446
country ==CANADA	1.7	0.5867
country ==BELGIUM	1.67	0.5997
country ==SWITZERLAND	1.66	0.6011
country ==FINLAND	1.63	0.6133
ATC1 == M	1.61	0.6214
year == 2000	1.6	0.6240
year == 2001	1.59	0.6284

	Semi-Parametric	
	Model 4	
Variable	VIF	1/VIF
L3_ln_pr_SU_atc4Ctry_	2.92	0.3425
L3_ln_SU_atc4Ctry_	2.9	0.3453
ATC1 == L	2.23	0.4491
country ==JAPAN	2.21	0.4516
country ==TURKEY	2.17	0.4605
ATC1 == N	2.13	0.4685
country ==POLAND	2.06	0.4849
ATC1 == J	2.05	0.4878
country ==SAFRICA	1.95	0.5133
country ==ITALY	1.87	0.5351
country ==FRANCE	1.85	0.5401
country ==GREECE	1.83	0.5456
country ==CANADA	1.7	0.5871
country ==BELGIUM	1.67	0.6001
country ==SWITZERLAND	1.66	0.6022
country ==FINLAND	1.62	0.6156
ATC1 == M	1.6	0.6240
year == 2000	1.6	0.6258
year == 2001	1.59	0.6305
country ==PORTUGAL	1.57	0.6374
ATC1 == S	1.55	0.6447

ATC1 == S	1.57	0.6360
country ==PORTUGAL	1.57	0.6373
ATC1 == B	1.57	0.6389
country ==AUSTRIA	1.56	0.6418
year == 2002	1.56	0.6422
country ==SPAIN	1.54	0.6502
year == 2003	1.54	0.6513
ATC1 == G	1.52	0.6589
country ==GERMANY	1.49	0.6705
year == 2004	1.48	0.6749
country ==UK	1.48	0.6758
ATC1 == C	1.46	0.6837
country ==US	1.46	0.6866
year == 2005	1.43	0.6969
country ==SWEDEN	1.4	0.7126
year == 2006	1.38	0.7267
country ==NETHERLANDS	1.36	0.7372
ATC1 == H	1.31	0.7634
ATC1 == R	1.28	0.7797
ATC1 == D	1.26	0.7925
year == 2007	1.22	0.8228
ATC1 == V	1.17	0.8556
year == 2008	1.08	0.9250
Mean VIF	2.04	

year == 2002	1.55	0.6463
country ==AUSTRIA	1.55	0.6470
ATC1 == B	1.54	0.6485
country ==SPAIN	1.53	0.6517
year == 2003	1.52	0.6583
ATC1 == G	1.52	0.6591
country ==GERMANY	1.49	0.6733
country ==UK	1.47	0.6799
ATC1 == C	1.46	0.6840
year == 2004	1.46	0.6873
country ==US	1.45	0.6905
country ==SWEDEN	1.4	0.7145
year == 2005	1.39	0.7190
country ==NETHERLANDS	1.35	0.7410
year == 2006	1.33	0.7509
ATC1 == H	1.3	0.7702
ATC1 == R	1.28	0.7812
ATC1 == D	1.25	0.7976
year == 2007	1.17	0.8513
ATC1 == V	1.16	0.8592
year == 2008	1.05	0.9565
Mean VIF	1.67	

Commands

```
xi: regress _d  L3_ln_pr_SU_atc4Ctry_ L3_ln_SU_atc4Ctry_  i.year i.atc1
i.countrynosector _t _t2
estat vif
```

C.3.2.2 Robustness Checks

Time Effects

Table C.11 Robustness Check: Time Effects

Variables	*Parameter Estimates by Cloglog (quadratic in t)*				*Marginal Effects in Cloglog (quadratic in t)*			
	1	2	3	4 (post-99)	1	2	3	4 (post-99)
Log Lagged Avg Non-Generic Price/SU in Ctry-ATC4	0.084*** [0.0150]	0.077*** [0.0152]	0.087*** [0.0151]	0.060** [0.0205]	0.003*** [0.0006]	0.003*** [0.0006]	0.003*** [0.0006]	0.003** [0.0009]
Log Lagged Total SU in Ctry-ATC4	0.065*** [0.0107]	0.061*** [0.0105]	0.067*** [0.0108]	0.058*** [0.0136]	0.003*** [0.0004]	0.002*** [0.0004]	0.003*** [0.0004]	0.003*** [0.0006]
Log Lagged Avg Non-Generic Price/SU in Ctry-ATC4 * ln(t)	-0.020** [0.0072]		-0.020** [0.0072]		-0.001** [0.0003]		-0.001** [0.0003]	
Log Lagged Total SU in Ctry-ATC4 * ln(t)	-0.015*** [0.0043]		-0.014*** [0.0042]		-0.001*** [0.0002]		-0.001*** [0.0002]	
First Launch Before 1999		-0.285*** [0.0775]	-0.282*** [0.0770]			-0.011*** [0.0029]	-0.011*** [0.0029]	
Years since global launch (t)	0.221*** [0.0417]	0.140*** [0.0289]	0.263*** [0.0427]	0.384*** [0.0594]	0.009*** [0.0017]	0.006*** [0.0012]	0.010*** [0.0017]	0.017*** [0.0027]
Years since global launch squared (t^2)	-0.024*** [0.0036]	-0.016*** [0.0027]	-0.024*** [0.0036]	-0.044*** [0.0099]	-0.001*** [0.0001]	-0.001*** [0.0001]	-0.001*** [0.0001]	-0.002*** [0.0004]
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Calendar Year Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Number of Observations	58530	58530	58530	34560	58530	58530	58530	34560
LogLikelihood	-10530.25	-10534.25	-10523.92	-6860.47	-10530.25	-10534.25	-10523.92	-6860.47
Akaike's Info Criteria	21154.507	21160.504	21143.849	13810.938	21154.507	21160.504	21143.849	13810.938
Bayesian Info Criteria	21576.44	21573.46	21574.76	14191.21	21576.44	21573.46	21574.76	14191.21

Note: *p<0.05, **p < 0.01, ***p<0.001. tandard errors clustered at molecule-country level (standard errors in brackets).
Non-exponentiated parameter estimates reported. Model 4 estimates are for molecules that launched globally after 1999

Table C.12 Robustness Check: Time Effects and Age of Therapeutic Class

Variables	*Parameter Estimates by Cloglog (quadratic in t)*	
	1	2
Log Lagged Avg Non-Generic Price/SU in Ctry-ATC4	0.121*** [0.02]	0.126*** [0.02]
Log Lagged Total SU in Ctry-ATC4	0.086*** [0.01]	0.089*** [0.01]
Log Lagged Avg Non-Generic Price/SU in Ctry-ATC4 * TherapClassAge	-0.013** [0.00]	-0.013** [0.00]
Log Lagged Total SU in Ctry-ATC4 * TherapClassAge	-0.006** [0.00]	-0.006** [0.00]
Log Lagged Avg Non-Generic Price/SU in Ctry-ATC4 * ln(t)		-0.006 [0.01]
Log Lagged Total SU in Ctry-ATC4 * ln(t)		-0.010* [0.00]
Years since global launch (t)	0.125*** [0.03]	0.197*** [0.04]
Years since global launch squared (t^2)	-0.017*** [0.00]	-0.022*** [0.00]
Country Dummies	Yes	Yes
ATC1 Dummies	Yes	Yes
Calendar Year Dummies	Yes	Yes
Number of Observations	55432	55432
LogLikelihood	-10054.95	-10051.72

Akaike's Info Criteria	20203.9043	20201.4446
Bayesian Info Criteria	20623.28	20638.67

Note: *p<0.05, **p < 0.01, ***p<0.001.
Standard errors clustered at molecule-country level (standard errors in brackets). Non-exponentiated parameter estimates reported .
Estimates for molecules that launched globally after 1993

Table C.13 Robustness Check: Market Structure and Competition

Variables	*Parameter Estimates by Cloglog (quadratic in t)*				*Marginal Effects in Cloglog (quadratic in t)*			
	1	2	3	4	1	2	3	4
Log Lagged Avg Price/SU	0.069*** [0.0160]	0.097*** [0.0238]	0.073*** [0.0162]	0.086*** [0.0163]	0.003*** [0.0007]	0.004*** [0.0009]	0.003*** [0.0007]	0.004*** [0.0007]
Log Lagged Total SU in Ctry-atc4	0.047*** [0.0113]	0.081*** [0.0148]	0.006 [0.0122]	0.016 [0.0126]	0.002*** [0.0005]	0.003*** [0.0006]	0 [0.0005]	0.001 [0.0005]
Log Molecule Concentration in Ctry-atc4 (IHH)	-0.065** [0.0236]	-0.039 [0.0273]	-0.004 [0.0252]	-0.008 [0.0253]	-0.003** [0.0010]	-0.002 [0.0011]	0 [0.0011]	0 [0.0010]
Log Number of Molecules with Generic Comp in Ctry-ATC4		-0.013 [0.0121]				0 [0.0005]		
Log Number of Molecules in Ctry-ATC4			0.281*** [0.0344]	0.278*** [0.0343]			0.012*** [0.0014]	0.012*** [0.0014]
Log Lagged Avg Price/SU * ln(t)				-0.021** [0.0074]				-0.001** [0.0003]
Log Lagged Total SU * ln(t)				-0.015*** [0.0043]				-0.001*** [0.0002]

First Launch Before 1999				-0.358*** [0.0865]				-0.014*** [0.0034]
Years since global launch (t)	0.080** [0.0270]	0.088** [0.0312]	0.082** [0.0273]	0.263*** [0.0438]	0.003** [0.0012]	0.003** [0.0012]	0.003** [0.0012]	0.011*** [0.0018]
Years since global launch squared (t2)	-0.014*** [0.0028]	-0.013*** [0.0030]	-0.015*** [0.0028]	-0.024*** [0.0037]	-0.001*** [0.0001]	-0.001*** [0.0001]	-0.001*** [0.0001]	-0.001*** [0.0002]
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calendar Year Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Number of Observations	54721	38098	54721	54721	54721	38098	54721	54721
LogLikelihood	-10290.07	-6731.46	-10246.68	-10225.81	-10290.07	-6731.46	-10246.68	-10225.81
Akaike's Info Crit	20672.15	13556.92	20587.35	20551.62	20672.146	13556.92	20587.35	20551.62
Bayesian Info Crit	21082.01	13958.68	21006.12	20997.12	21082.01	13958.68	21006.12	20997.12

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets). Non-exponentiated parameter estimates reported

Firm Characteristics

Table C. 14 Robustness Check: Firm Effects

Variables	*Parameter Estimates by Cloglog (quadratic in t)*				*Marginal Effects in Cloglog (quadratic in t)*			
	1	2	3	4	1	2	3	4
Log Lagged Avg Non-Generic Price/SU in Ctry-ATC4	0.069*** [0.0149]	0.071*** [0.0150]	0.073*** [0.0149]	0.082*** [0.0151]	0.003*** [0.0006]	0.003*** [0.0006]	0.003*** [0.0006]	0.003*** [0.0006]
Log Lagged Total SU in Ctry-ATC4	0.064*** [0.0106]	0.066*** [0.0107]	0.062*** [0.0105]	0.074*** [0.0110]	0.003*** [0.0004]	0.003*** [0.0004]	0.002*** [0.0004]	0.003*** [0.0004]
Log Firm Sales (global) in 2007	0.111*** [0.0126]			0.128*** [0.0140]	0.004*** [0.0005]			0.005*** [0.0005]
Log Number of Countries Firm has Launched in		0.217*** [0.0448]				0.009*** [0.0017]		
Log Local Firm Experience (number of molecules launched)		0.084*** [0.0162]				0.003*** [0.0006]		
Log Firm's Total Number of Molecules			0.074*** [0.0157]				0.003*** [0.0006]	
Domestic Launch			-0.04 [0.0913]	0.210* [0.1034]			-0.002 [0.0035]	0.009 [0.0047]
Log Lagged Avg Non-Generic Price/SU in Ctry-ATC4 * ln(t)				-0.020** [0.0072]				-0.001** [0.0003]

Log Lagged Total SU in Ctry-ATC4 * ln(t)				-0.015*** [0.0043]				-0.001*** [0.0002]
First Launch Before 1999				-0.344*** [0.0760]				-0.013*** [0.0028]
Years since global launch (t)	0.124*** [0.0268]	0.118*** [0.0266]	0.104*** [0.0265]	0.310*** [0.0430]	0.005*** [0.0011]	0.005*** [0.0011]	0.004*** [0.0011]	0.012*** [0.0017]
Years since global launch squared (t2)	-0.016*** [0.0028]	-0.016*** [0.0028]	-0.015*** [0.0027]	-0.026*** [0.0037]	-0.001*** [0.0001]	-0.001*** [0.0001]	-0.001*** [0.0001]	-0.001*** [0.0001]
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calendar Year Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Number of Observations	58521	58530	58530	58521	58521	58530	58530	58521
LogLikelihood	-10487.9	-10502.04	-10526.97	-10463.85	-10487.9	-10502.04	-10526.97	-10463.85
Akaike's Info Crit	21067.8	21098.1	21147.9	21027.7	21067.8	21098.1	21147.9	21027.7
Bayesian Info Crit	21480.7	21520.0	21569.9	21476.6	21480.7	21520.0	21569.9	21476.6

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets). Non-exponentiated parameter estimates reported

Molecule Characteristics

Table C.15 Robustness Check: Molecule Characteristics

Variables	*Parameter Estimates by Cloglog (quadratic in t)*				*Marginal Effects in Cloglog (quadratic in t)*			
	1	2	3	4	1	2	3	4
Log Lagged Price/SU	0.068*** [0.0151]	0.072*** [0.0152]	0.060*** [0.0151]	0.084*** [0.0153]	0.003*** [0.0006]	0.003*** [0.0006]	0.002*** [0.0006]	0.003*** [0.0006]
Log Lagged Total SU in Ctry-ATC4	0.053*** [0.0105]	0.053*** [0.0105]	0.054*** [0.0105]	0.062*** [0.0109]	0.002*** [0.0004]	0.002*** [0.0004]	0.002*** [0.0004]	0.002*** [0.0004]
Log Global Molecule Sales	0.074*** [0.0128]				0.003*** [0.0005]			
Log Molecule's Global Reach		1.521*** [0.1544]		1.531*** [0.1530]		0.059*** [0.0059]		0.059*** [0.0058]
Log Markets Launched in at t			-0.387*** [0.0443]				-0.015*** [0.0017]	
Log Lagged Avg Price/SU * ln(t)				-0.021** [0.0073]				-0.001** [0.0003]
Log Lagged Total SU * ln(t)				-0.015*** [0.0042]				-0.001*** [0.0002]
First Launch Before 1999				-0.276*** [0.0769]				-0.010*** [0.0028]
Years since global launch (t)	0.100*** [0.0264]	0.105*** [0.0267]	-0.085** [0.0327]	0.276*** [0.0430]	0.004*** [0.0011]	0.004*** [0.0011]	-0.003** [0.0013]	0.011*** [0.0017]

Years since global launch squared	-0.015*** [0.0027]	-0.017*** [0.0028]	-0.003 [0.0029]	-0.026*** [0.0036]	-0.001*** [0.0001]	-0.001*** [0.0001]	0 [0.0001]	-0.001*** [0.0001]
Number of Obs	58279	58530	58229	58530	58279	58530	58229	58530
LogLikelihood	-10433	-10485	-10478	-10467	-10433	-10485	-10478	-10467
Akaike's Info Crit	20958	21061	21049	21031	20958	21061	21049	21031
Bayesian Info Crit	21370	21474	21461	21471	21370	21474	21461	21471

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets). Non-exponentiated parameter estimates reported. Country, ATC1 and calendar-year dummies included

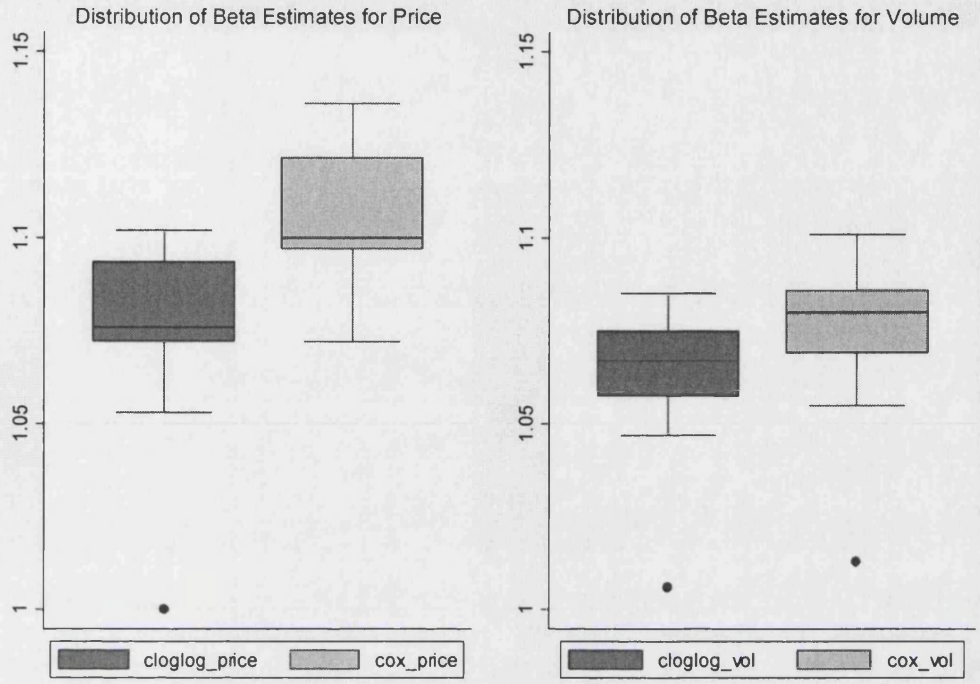
Regulation: EU Subsample

Table C.16 Robustness Check: Regulation EU subsample

Variables	*Parameter Estimates by Cloglog (quadratic in t)*			*Marginal Effects by Cloglog (quadratic in t)*		
	1	2	3 (post-99)	1	2	3 (post-99)
Log Lagged Avg Price/SU	0.096*** [0.017]	0.096*** [0.017]	0.102*** [0.022]	0.004*** [0.0007]	0.004*** [0.0007]	0.005*** [0.0010]
Log Lagged Total SU	0.072*** [0.012]	0.072*** [0.0124]	0.079*** [0.0162]	0.003*** [0.0005]	0.003*** [0.0005]	0.004*** [0.0007]
External Referencing	-0.574*** [0.12]			-0.030*** [0.008]		
High Price EU		0.823*** [0.1322]	0.913*** [0.19]		0.042*** [0.008]	0.051*** [0.013]
Years since global launch (t)	0.154*** [0.0341]	0.154*** [0.0341]	0.574*** [0.0683]	0.007*** [0.0015]	0.007*** [0.0015]	0.026*** [0.0032]
Years since global launch squared (t^2)	-0.021*** [0.0035]	-0.021*** [0.0035]	-0.068*** [0.0122]	-0.001*** [0.0002]	-0.001*** [0.0002]	-0.003*** [0.0006]
Number of Obs	39189	39189	23767	39189	39189	23767
LogLikelihood	-7420.85	-7420.85	-4899.87	-7420.85	-7420.85	-4899.87
Akaike's Info Crit	14919.69	14919.69	9877.746	14919.69	14919.69	9877.746
Bayesian Info Crit	15254.16	15254.16	10192.71	15254.16	15254.16	10192.71

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets). Non-exponentiated parameter estimates reported . Country, ATC1 and calendar-year dummies included

Figure C.1 Distribution of Parameter Estimates



Note: Cloglog with quadratic duration dependence

Table C.17 Descriptive statistics for parameter estimates of expected price

Variable	*Obs*	*Mean*	*Std. Dev.*	*Min*	*Max*
cloglog_price	16	1.0715	0.030945	1	1.102
cox_price	16	1.106938	0.016834	1.072	1.136

Table C.18 Descriptive statistics for parameter estimates of expected volume

Variable	*Obs*	*Mean*	*Std. Dev.*	*Min*	*Max*
cloglog_vol	16	1.063125	0.018743	1.006	1.085
cox_vol	16	1.075687	0.02162	1.013	1.101

Appendix C.4: Supplementary Data

Table C.19 Populations of Countries in 000s

Country	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Australia	18,925.86	19,153.38	19,413.24	19,651.44	19,895.44	20,127.36	20,394.79	20,697.88	21,015.04	21,015.69
Austria	7,992.32	8,011.57	8,043.05	8,083.80	8,117.75	8,174.73	8,233.31	8,281.95	8,315.38	8,337.61
Belgium	10,226.42	10,251.25	10,286.57	10,332.78	10,376.13	10,421.13	10,478.62	10,547.96	10,625.70	10,692.72
Canada	30,403.88	30,689.04	31,021.25	31,372.59	31,676.08	31,995.20	32,312.08	32,649.48	32,976.03	33,095.00
Finland	5,165.47	5,176.20	5,188.01	5,200.60	5,213.01	5,228.17	5,246.10	5,266.27	5,288.72	5,306.84
France	58,673.08	59,049.35	59,454.45	59,863.27	60,264.20	60,643.30	60,995.91	61,352.57	61,707.07	61,840.27
Germany	82,100.24	82,211.51	82,349.93	82,488.50	82,534.18	82,516.26	82,469.42	82,376.45	82,247.02	82,772.16
Greece	10,882.61	10,917.46	10,949.95	10,987.56	11,023.53	11,061.74	11,103.93	11,148.53	11,192.85	11,217.71
Italy	56,911.68	56,937.01	56,971.67	57,151.03	57,597.22	58,166.89	58,597.42	58,930.67	59,336.39	58,851.26
Japan	126,686	126,925.84	127,291	127,435.0	127,619	127,687.	127,768	127,769.5	127,770.8	127,567.9
Netherlands	15,812.09	15,925.51	16,046.18	16,148.92	16,225.30	16,281.78	16,319.87	16,346.10	16,381.69	16,389.96
Poland	38,270.00	38,258.48	38,248.08	38,232.30	38,195.18	38,180.25	38,161.31	38,132.28	38,115.97	37,926.87
Portugal	10,171.95	10,225.84	10,293.00	10,368.41	10,441.07	10,501.97	10,549.42	10,584.34	10,608.33	10,619.69
Spain	39,927.22	40,264.16	40,721.45	41,314.02	42,004.58	42,691.75	43,398.19	44,068.24	44,873.57	44,310.87
Sweden	8,857.88	8,872.11	8,895.96	8,924.96	8,958.23	8,993.53	9,029.57	9,080.51	9,148.09	9,195.18
Switzerland	7,144.00	7,184.25	7,229.85	7,284.76	7,339.00	7,389.63	7,437.11	7,483.93	7,550.02	7,617.04
Turkey	66,337.99	67,392.50	68,366.83	69,304.05	70,231.02	71,151.01	72,064.99	72,971.47	73,875.00	74,767.00
UK	58,684.43	58,886.07	59,113.50	59,323.50	59,557.34	59,845.84	60,238.38	60,587.35	60,975.36	61,411.69
US	279,040.2	282,194.31	285,112.03	287,888.0	290,447.6	293,191.5	295,895.9	298,754.8	301,621.2	303,597.7

Source: http://stats.oecd.org/WBOS

Table C.20 Percentage of the Total Population aged 65 and over

Country	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Australia	12.34	12.42	12.55	12.64	12.73	12.83	12.93	13.01	13.16	13.71
Austria	15.41	15.43	15.47	15.48	15.48	15.74	16.26	16.69	17.03	17.26
Belgium	16.68	16.80	16.90	16.98	17.07	17.17	17.22	17.16	17.08	17.07
Canada	12.45	12.55	12.65	12.73	12.84	12.96	13.08	13.24	13.41	13.63
Finland	14.77	14.92	15.08	15.25	15.46	15.72	15.94	16.23	16.49	16.63
France	15.94	16.06	16.16	16.24	16.30	16.38	16.44	16.44	16.47	16.50
Germany	16.09	16.45	16.85	17.28	17.75	18.32	18.94	19.53	19.93	20.06
Greece	16.31	16.63	17.00	17.36	17.69	17.98	18.32	18.54	18.60	18.57
Italy	17.97	18.27	18.56	18.86	19.12	19.35	19.60	19.84	20.00	20.28
Japan	16.72	17.37	17.96	18.54	19.05	19.48	20.16	20.82	21.49	22.11
Netherlands	13.54	13.58	13.63	13.68	13.78	13.94	14.15	14.37	14.60	14.86
Poland	12.03	12.24	12.47	12.71	12.86	13.05	13.21	13.35	13.44	13.40
Portugal	15.92	16.20	16.45	16.61	16.75	16.91	17.07	17.19	17.34	16.93
Spain	16.61	16.82	16.93	16.94	16.89	16.83	16.75	16.69	16.64	16.99
Sweden	17.33	17.26	17.22	17.18	17.16	17.21	17.27	17.33	17.43	17.69
Switzerland	15.22	15.34	15.49	15.61	15.66	15.77	15.91	16.10	16.31	16.54
Turkey	5.32	5.38	5.43	5.51	5.62	5.75	5.88	5.97	6.04	6.12
UK	15.81	15.81	15.86	15.91	15.96	15.99	16.00	15.99	16.04	16.17
US	12.47	12.43	12.39	12.36	12.38	12.38	12.42	12.47	12.56	12.74

Source: http://stats.oecd.org/WBOS

Table C.21 Life expectancy at birth in years: total

Country	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Australia	79.0	79.3	79.7	80.0	80.3	80.6	80.9	81.1	81.3	81.5
Austria	77.8	78.1	78.6	78.8	78.8	79.3	79.5	79.9	80.1	80.3
Belgium	77.7	77.8	78.1	78.2	78.2	78.9	79.1	79.5	79.7	79.9
Canada	79.0	79.3	79.6	79.7	79.9	80.2	80.4	80.6	80.8	81.0
Finland	77.5	77.7	78.2	78.3	78.5	79.0	79.1	79.5	79.7	79.9
France	78.9	79.2	79.3	79.4	79.3	80.3	80.2	80.9	81.1	81.3
Germany	77.9	78.2	78.5	78.5	78.6	79.2	79.4	79.8	80.0	80.2
Greece	78.1	78.0	78.5	78.7	78.9	79.1	79.3	79.6	79.8	80.0
Italy	79.7	80.0	80.2	80.3	80.0	80.9	80.9	81.1	81.3	81.5
Japan	80.6	81.2	81.5	81.8	81.9	82.1	82.0	82.4	82.6	82.8
Netherlands	77.9	78.0	78.3	78.4	78.6	79.2	79.4	79.8	80.0	80.2
Poland	72.7	73.9	74.3	74.6	74.7	75.0	75.1	75.3	75.5	75.7
Portugal	76.2	76.7	77.0	77.2	77.4	78.3	78.1	78.9	79.1	79.3
Spain	78.9	79.4	79.7	79.8	79.7	80.3	80.4	81.1	81.3	81.5
Sweden	79.5	79.7	79.9	79.9	80.2	80.6	80.6	80.8	81.0	81.2
Switzerland	79.8	79.9	80.4	80.6	80.6	81.2	81.4	81.7	81.9	82.1
Turkey	69.5	70.5	70.6	70.8	71.0	71.2	71.4	71.6	71.8	72.0
UK	77.5	77.9	78.2	78.3	78.4	78.9	79.1	79.3	79.5	79.7
US	76.7	76.8	77.1	77.2	77.5	77.8	77.8	78.0	78.2	78.4

Source: http://stats.oecd.org/WBOS (Values for 2006 (Canada, Italy and UK only), 2007, 2008 found by exponential smoothing with alpha = 0.95)

Table C. 22 GDP per capita

Country	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Australia	26128.00	27232.66	28280.91	29610.50	31138.58	32429.03	33962.76	35666.18	37564.68	38171.90
Austria	27010.57	28736.22	28803.54	30224.83	31096.03	32589.24	33495.73	35259.30	37119.30	37722.37
Belgium	25299.27	27540.44	28435.39	29946.22	30146.26	31035.17	32063.15	33608.19	35382.25	35960.22
Canada	27135.32	28446.91	29334.25	29893.27	31241.85	32811.47	35002.25	36867.06	38500.34	39172.12
Finland	23697.79	25652.66	26652.45	27592.09	27703.31	29905.30	30695.44	32586.09	34717.98	35206.25
France	23615.51	25232.35	26643.27	27771.66	27409.80	28305.25	29758.69	31054.96	32686.29	33223.03
Germany	25141.67	25918.96	26861.69	27587.16	28579.34	29911.91	31379.56	32834.94	34390.73	34981.27
Greece	17031.88	18388.86	19933.54	21597.60	22577.14	24173.48	24928.09	26700.57	28422.97	28820.41
Italy	24196.44	25564.66	27133.58	26803.97	27149.36	27426.42	28122.31	29356.23	30381.22	30968.92
Japan	24252.39	25592.96	26194.58	26813.52	27483.13	29038.71	30310.34	32040.05	33626.15	34184.52
Netherlands	26932.89	29371.44	30795.78	31943.50	31716.39	33221.37	35110.66	37130.15	39224.72	39831.53
Poland	9996.32	10554.74	10953.15	11562.62	11990.23	13019.50	13785.77	14841.96	15988.54	16177.77
Portugal	16113.29	17066.80	17804.43	18446.85	18799.47	19178.42	20656.24	21656.33	22815.40	23182.19
Spain	19824.41	21295.34	22596.91	24066.50	24759.06	25967.88	27376.76	29519.98	31585.74	31994.16
Sweden	25800.81	27725.55	27970.84	29003.77	30075.94	32078.04	32298.10	34455.59	36603.11	37133.76
Switzerland	30210.38	31778.01	32473.09	33792.81	33695.78	34971.93	35839.14	38568.28	41101.45	41665.95
Turkey	8046.33	8724.35	8178.01	8216.67	8316.42	9595.48	10840.82	12074.14	12993.29	13136.67
UK	24248.96	26041.06	27585.03	28888.07	29863.24	31746.92	32694.74	34136.67	35668.88	36299.51
US	32994.19	34573.86	35307.95	36145.24	37489.17	39608.85	41718.04	43838.72	45488.88	46335.89

(unit of measure: US dollars, PPPs. Values for 2008 found by exponential smoothing with alpha = 0.85)

Source: http://webnet.oecd.org/wbos/

Table C.23 GDP deflators used to calculate real sales figures

Country	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Australia	96.17	100	104.01	106.59	110.38	114.15	119.23	124.67	129.57	134.65
Austria	98.26	100	101.76	103.22	104.44	106.59	108.51	110.43	112.93	115.65
Belgium	98.15	100	101.99	103.89	105.59	108.18	110.79	113.05	114.92	118.11
Canada	96.03	100	101.12	102.22	105.58	108.99	112.65	115.31	118.94	121.12
Finland	97.45	100	103.03	104.34	103.92	104.58	105.02	106.34	109.01	110.5
France	98.47	100	101.91	104.39	106.33	107.8	109.69	112.43	114.93	117.32
Germany	100.6	100	101.2	102.63	103.9	105.06	105.84	106.43	108.34	109.48
Greece	94.65	100	102.71	106.51	110.2	113.97	117.69	121.7	125.52	129.82
Italy	98.02	100	102.96	106.31	109.62	112.51	114.86	116.86	119.51	122.97
Japan	101.76	100	98.77	97.24	95.69	94.66	93.5	92.59	91.9	91.22
Netherlands	96.04	100	105.1	109.12	111.5	112.31	114.65	116.85	118.55	121.4
Poland	93.22	100	103.47	105.8	106.21	110.56	113.48	115.16	118.58	121.83
Portugal	97.06	100	103.67	107.76	111.16	113.88	116.77	119.97	123.54	126.63
South Africa	91.9	100	107.67	119	124.48	131.39	138.2	148.15	161.37	176.07
Spain	96.67	100	104.2	108.69	113.19	117.75	122.74	127.61	131.55	135.75
Sweden	98.55	100	102.3	103.96	105.98	106.23	107.15	109.13	112.78	115.94
Switzerland	98.88	100	100.8	101.27	102.28	102.87	103.17	104.78	106.28	107.34
Turkey	67.01	100	152.85	210.05	258.94	291.04	311.66	340.74	367.74	391.7
UK	98.72	100	102.2	105.39	108.61	111.4	113.97	117	120.56	123.68
US	97.87	100	102.4	104.19	106.4	109.46	113	116.57	119.68	122.09

Source: International Monetary Fund, World Economic Outlook Database, April 2008.

Table C.24 Corruption Perception Indexes of Countries in the Dataset

Country	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Australia	8.7	8.3	8.5	8.6	8.8	8.8	8.8	8.7	8.6	8.7
Austria	7.6	7.7	7.8	7.8	8	8.4	8.7	8.6	8.1	8.1
Belgium	5.3	6.1	6.6	7.1	7.6	7.5	7.4	7.3	7.1	7.3
Canada	9.2	9.2	8.9	9	8.7	8.5	8.4	8.5	8.7	8.7
Finland	9.8	10	9.9	9.7	9.7	9.7	9.6	9.6	9.4	9
France	6.6	6.7	6.7	6.3	6.9	7.1	7.5	7.4	7.3	6.9
Germany	8	7.6	7.4	7.3	7.7	8.2	8.2	8	7.8	7.9
Greece	4.9	4.9	4.2	4.2	4.3	4.3	4.3	4.4	4.6	4.7
Italy	4.7	4.6	5.5	5.2	5.3	4.8	5	4.9	5.2	4.8
Japan	6	6.4	7.1	7.1	7	6.9	7.3	7.6	7.5	7.3
Netherlands	9	8.9	8.8	9	8.9	8.7	8.6	8.7	9	8.9
Poland	4.2	4.1	4.1	4	3.6	3.5	3.4	3.7	4.2	4.6
Portugal	6.7	6.4	6.3	6.3	6.6	6.3	6.5	6.6	6.5	6.1
Spain	6.6	7	7	7.1	6.9	7.1	7	6.8	6.7	6.5
Sweden	9.4	9.4	9	9.3	9.3	9.2	9.2	9.2	9.3	9.3
Switzerland	8.9	8.6	8.4	8.5	8.8	9.1	9.1	9.1	9	9
Turkey	3.6	3.8	3.6	3.2	3.1	3.2	3.5	3.8	4.1	4.6
UK	8.6	8.7	8.3	8.7	8.7	8.6	8.6	8.6	8.4	7.7
USA	7.5	7.8	7.6	7.7	7.5	7.5	7.6	7.3	7.2	7.3

Source: http://www.transparency.org/policy_research/surveys_indices/cpi/
* CPI Score relates to perceptions of the degree of corruption as seen by business people and country analysts, and ranges between 10 (highly clean) and 0 (highly corrupt).

Table C.25 Pricing Schemes in the European markets

Country	*Pricing Policy*			*Reimbursement Lists*		*Reference Price System*		
	Ext Ref [a]	*Int Ref* [b]	*Pricing Policy*	*+ List*	*- List*	*RPS*	*Year Introduced*	*Clusters*
Austria	1	1	Statutory	1	0	0	-	-
Belgium	1	1	Statutory	1	0	1	2001	ATC5
Finland	1	1	Statutory	1	1	0	-	-
France	1	1	Negotiation	1	0	1	2003	ATC5
Germany	0	0	None	0	1	1	1989	ATC4,5
Greece	1	1	Statutory	0	1	1	2006	- **
Italy	1	1	Negotiation	1	0	1	2001	ATC5
Netherlands	1	0	Statutory	1	0	1	1991	ATC3,4,5
Poland	1	1	Statutory	1	0	1	1998	ATC3,4,5
Portugal	1	1	Statutory	1	0	1	2003	ATC5
Spain	1	1	Negotiation	1	1	1	2000	ATC5
Sweden	0	0	Statutory	1	0	0	1993*	-
Switzerland	1	1	Statutory	1	0	1	2003	ATC5
UK	0	1	None	0	1	0	-	-
Turkey	1	1	Statutory	1	0	1	2004	ATC5

[a] External Referencing, [b] Internal Referencing

*Ref Price System Abolished in 2002

** Methodology has not been defined

APPENDIX D: Appendix to Chapter 4

Table D.1 Market Environment for Generic Medicines

	USA	EU
Generic Medicines as a % of Total Market	63%	42%
Basic Product Patent	20 yrs	20 yrs
Data Exclusivity (Blocks market authorization procedures for generics)	5 years	8+2+(1) years
Patent Extensions (SPC etc)	14 yrs max	15 yrs
Bolar Provision (right to perform generic R&D before patent expiration)	Yes since 1984	Yes since 2004
Immediate Generic Competition (Upon patent expiration)	Yes	No (due to P&R procedures)
Fees for Generic Registration	No	Yes (80,000-120,000 €)
Free Price Competition	Yes	No (not in most states)
Harmonized Regulatory and IP Requirements	Yes	No

Source : (Perry 2009)

Table D.2 Number of generic molecules that launched in each market –by local generic launch date

	1981-1985	1986-1989	1990-1995	1996-1999	2000-2004	2005-2008	Total
AUSTRALIA	3	5	23	23	34	36	124
AUSTRIA	6	3	17	12	37	38	113
BELGIUM	1	2	8	7	31	29	78
CANADA	1	10	34	35	39	38	157
FINLAND	4	7	12	11	32	32	98
FRANCE		9	14	17	39	40	119
GERMANY	8	9	31	25	38	39	150
GREECE	11	15	16	19	24	32	117
ITALY	14	6	8	13	32	47	120
JAPAN	6	2	26	9	33	33	109
NETHERLANDS	5	6	24	24	35	21	115
POLAND			34	29	55	48	166
PORTUGAL	6	9	16	10	32	33	106
SAFRICA	1	4	13	15	43	40	116
SPAIN	3	12	15	21	27	40	118
SWEDEN	2	7	12	12	30	26	89
SWITZERLAND	5	3	11	12	18	36	85
TURKEY	3	14	28	25	29	46	145
UK	9	8	19	18	69	40	163
US	12	21	32	35	64	51	215

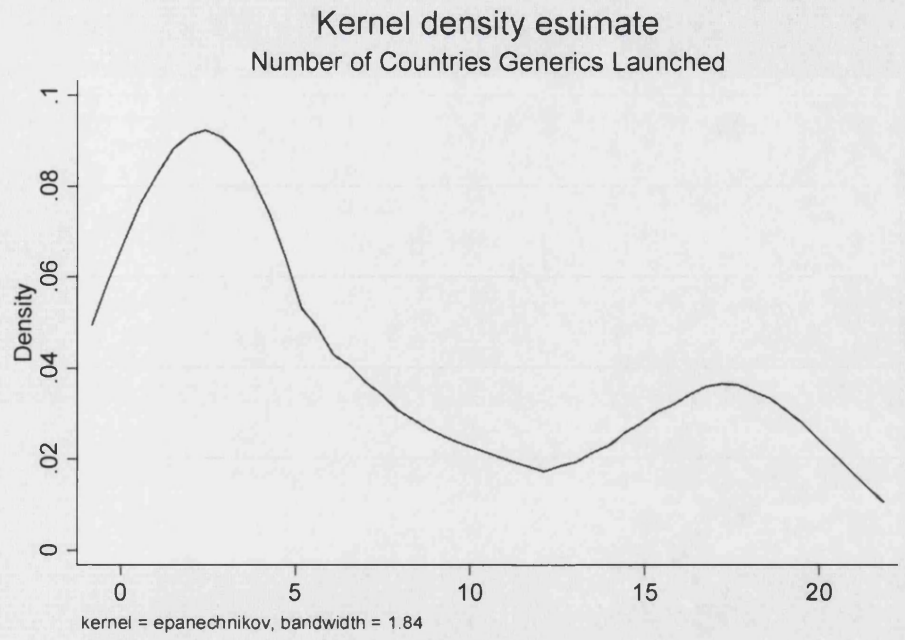


Figure D.1 Distribution of the number of countries where molecules in the dataset have launched

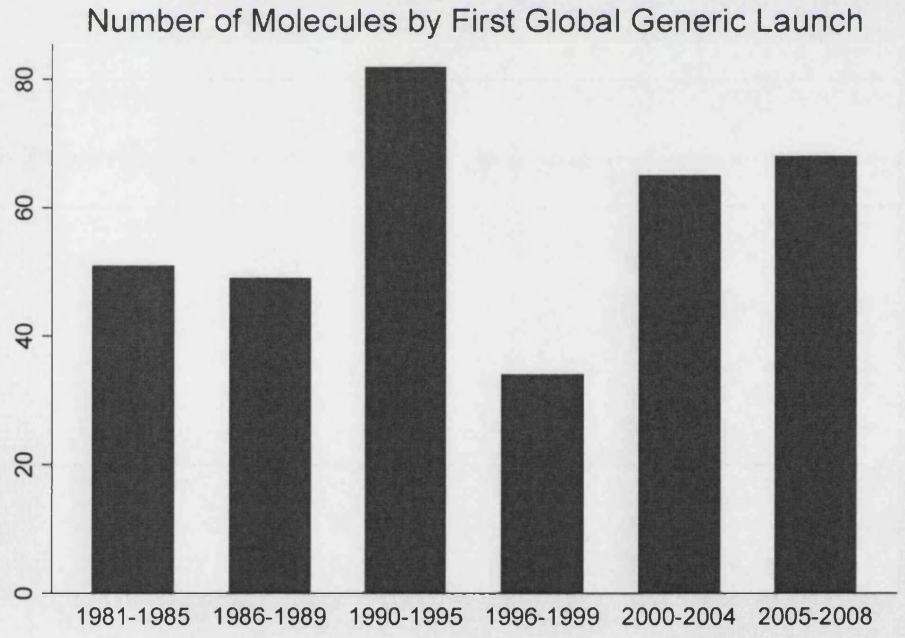


Figure D.2 The number of molecules by first global generic launch

Appendix D.1: Logistic Regression for Discrete Time Survival Analysis

The logistic model for discrete time specifications in survival analysis was primarily developed to analyse intrinsically discrete survival times, but it can also be applied to model the discrete time representation of a continuous time proportional hazards model. Logistic model is interpreted in terms of the proportional odds of failure (Singer and Willett 1993). Assuming monthly discrete intervals, the proportional odds model assumes that the relative odds of making a transition for individual *j* in month *t*, given survival up to end of the previous month, is given by:

$$\frac{h(t,\mathbf{z}_j)}{1-h(t,\mathbf{z}_j)}=\left[\frac{h_0(t)}{1-h_0(t)}\right]\exp(\mathbf{z}_j\boldsymbol{\beta}),$$

where $h(t,\mathbf{z}_j)$ is the discrete time hazard for month (interval) t for individual j, and $h_0(t)$ is the baseline hazard when $\mathbf{z}_j=\mathbf{0}$. Analogously to the proportional hazards model, the relative odds of failing is equal to the product of 1) a baseline relative odd common to all individuals $h_0(t)/[1-h_0(t)]$ and 2) an individual specific scaling factor, $\exp(\mathbf{z}_j\boldsymbol{\beta})$. Taking logs:

$$\text{logit}\,h(t,\mathbf{z}_j)=\ln\left\{\left[\frac{h_0(t)}{1-h_0(t)}\right]\exp(\mathbf{z}_j\boldsymbol{\beta})\right\}=\ln\left[\frac{h_0(t)}{1-h_0(t)}\right]+\mathbf{z}_j\boldsymbol{\beta}=\gamma_t+\mathbf{z}_j\boldsymbol{\beta},$$

where $\gamma_t=\text{logit}\,h_0(t)=\ln\{h_0(t)/[1-h_0(t)]\}$.

The expression $\text{logit}\,h(t,\mathbf{z}_j)=\ln\left[\frac{h(t,\mathbf{z}_j)}{1-h(t,\mathbf{z}_j)}\right]=\gamma_t+\mathbf{z}_j\boldsymbol{\beta}$ can be alternatively written to define the *logistic hazard model* as:

$$h(t,\mathbf{z}_j)=\frac{1}{1+\exp(-\gamma_t-\mathbf{z}_j\boldsymbol{\beta})}.$$

In practice, it has been shown that if cloglog and logistic hazard models for discrete time survival analysis share the same duration dependence and covariate vector and the hazard rate is relatively small, then the estimates they yield are similar. This can be

illustrated by writing the hazard rates in each model as a power series and using $G=\exp\left(\gamma_t+\mathbf{z}_j\boldsymbol{\beta}\right)$ (see Table D.3). When the probability of failure in each interval is small (i.e. $h\leq 0.10$ or less), then

$\gamma_t+\mathbf{z}_j\boldsymbol{\beta}=\log\left[-\log\left(1-h\right)\right]\leq -2.25$ in the cloglog model, and

$\gamma_t+\mathbf{z}_j\boldsymbol{\beta}=\log\left[\frac{h}{1-h}\right]\leq -2.20$ in the logistic model. In this case,

$G=\exp\left(\gamma_t+\mathbf{z}_j\boldsymbol{\beta}\right)=\approx\exp\left(-2.2\right)\approx 0.10$ and terms of the order G^2 and higher are close to zero and $\left(1-h\right)$ can be approximated by $\left(1-G\right)$ both for the cloglog and logit model. In the instances where the hazard is small, therefore, the parameters of the logistic model and the proportional hazard model will be nearly equal (Abbott 1985; Jenkins 2005).

Table D.3 Comparison of Cologlog and Logit Models

	Cloglog model	*Logit model*
$\gamma_t+\mathbf{z}_j\boldsymbol{\beta}=$	$\log\left[-\log\left(1-h\right)\right]$	$\log\left[\frac{h}{1-h}\right]$
$1-h=$	$1-G+\frac{G^2}{2!}-\frac{G^3}{3!}\ldots+\frac{(-1)^nG^n}{n!}\ldots$	$1-G+G^2-G^3\ldots+(-1)^nG^n\ldots$
$h\left(t,\mathbf{z}_j\right)=$	$1-\exp\left(-\exp\left(\gamma_t+\mathbf{z}_j\boldsymbol{\beta}\right)\right)$	$\frac{1}{1+\exp(-\gamma_t-\mathbf{z}_j\boldsymbol{\beta})}$
$\partial h/\partial z_i=$	$\exp\left\{-\exp\left(\mathbf{z}_j\boldsymbol{\beta}+\gamma_t\right)\right\}\exp\left(\mathbf{z}_j\boldsymbol{\beta}+\gamma_t\right)\beta_i$	$=\frac{\beta_i\exp(\mathbf{z}_j\boldsymbol{\beta}+\gamma_t)}{\left[1+\exp(\mathbf{z}_j\boldsymbol{\beta}+\gamma_t)\right]^2}$

Note: $G=\exp\left(\gamma_t+\mathbf{z}_j\boldsymbol{\beta}\right)$

Marginal Effects

The marginal effect of h with respect to $\mathbf{z}_j$ in the cloglog model is given by:

$\frac{\partial h}{\partial z_j} = \exp\left\{-\exp\left(\mathbf{z}_j\boldsymbol{\beta}+\gamma_t\right)\right\}\exp\left(\mathbf{z}_j\boldsymbol{\beta}+\gamma_t\right)\beta_j$, which implies that the marginal effect has the same sign as the parameter estimate.

For the logit model the marginal effect of the covariate z_i on the hazard h can be found by:

$$h_j(t) = \frac{1}{\left[1+\exp(-(\mathbf{z}_j\boldsymbol{\beta}+\gamma_t))\right]}$$

Let $u = 1+\exp(-(\mathbf{z}_j\boldsymbol{\beta}+\gamma_t))$ and $h = \frac{1}{u}$; $\partial h/\partial z_i = \frac{\partial h}{\partial u}\frac{\partial u}{\partial z_i}$

$$\frac{\partial h}{\partial u}\frac{\partial u}{\partial z_i} = \left\{-\frac{1}{\left[1+\exp(-(\mathbf{z}_j\boldsymbol{\beta}+\gamma_t))\right]^2}\right\}\left\{-\beta_i\exp(-(\mathbf{z}_j\boldsymbol{\beta}+\gamma_t))\right\} = \frac{\beta_i\exp(-(\mathbf{z}_j\boldsymbol{\beta}+\gamma_t))}{\left[1+\exp(-(\mathbf{z}_j\boldsymbol{\beta}+\gamma_t))\right]^2}$$

$$\partial h/\partial z_i = \frac{\beta_i\exp(-(\mathbf{z}_j\boldsymbol{\beta}+\gamma_t))}{\left[1+\exp(-(\mathbf{z}_j\boldsymbol{\beta}+\gamma_t))\right]^2} = \frac{\beta_i\exp(\mathbf{z}_j\boldsymbol{\beta}+\gamma_t)}{\left[1+\exp(\mathbf{z}_j\boldsymbol{\beta}+\gamma_t)\right]^2}.$$

Appendix D.2: Data Analysis

D.2.1 Empirical Results

Table D.4 Parametric Duration Dependence: Coefficients for Base Case Cloglog and Logit Estimates for First Generic Launch

Variables	*with year dummies*						*no year dummies*					
	CLOGLOG			LOGIT			CLOGLOG			LOGIT		
	1	2	3	1	2	3	1	2	3	1	2	3
Expected Generic Price												
LMAvgExpPg	0.092*	0.139*		0.091*	0.143*		0.101**	0.210***		0.102**	0.218***	
	[0.0369]	[0.0604]		[0.0383]	[0.0623]		[0.0363]	[0.0630]		[0.0372]	[0.0645]	
LMAvg_Pb			0.091*			0.090*			0.095**			0.096**
			[0.0368]			[0.0381]			[0.0359]			[0.0367]
medRatioPgPb			0.386			0.477			-0.914			-1
			[0.8662]			[0.9048]			[0.9538]			[0.9769]
Expected Market Size												
ExpMarketSizeUSD	0.122**			0.129**			0.198***			0.207***		
	[0.0456]			[0.0472]			[0.0480]			[0.0490]		
ExpMarketSizeSU		0.057			0.062			0.118*			0.125**	
		[0.0435]			[0.0457]			[0.0469]			[0.0483]	
LMAvg_USD_molCtr_			0.117*			0.124**			0.153**			0.160***
			[0.0456]			[0.0473]			[0.0465]			[0.0473]
avgGenShare_USD_			0.003			0			0.086***			0.088***
			[0.0159]			[0.0163]			[0.0141]			[0.0143]
Competition												
NumGenFirmMed	-1.763	-1.753	-1.756	-1.64	-1.633	-1.654	6.095***	6.238***	5.031***	6.239***	6.381***	5.164***
	[0.9894]	[0.9870]	[0.9836]	[1.0217]	[1.0187]	[1.0157]	[0.9547]	[0.9510]	[0.9023]	[0.9707]	[0.9670]	[0.9168]

Molecule Characteristics												
ln_lag_yrs	0.128*	0.113	0.126*	0.134*	0.118	0.132*	0.027	0.009	0.048	0.029	0.01	0.049
	[0.0619]	[0.0616]	[0.0619]	[0.0639]	[0.0635]	[0.0640]	[0.0597]	[0.0599]	[0.0597]	[0.0609]	[0.0611]	[0.0608]
ln_MolGlobalUSDAnnual_	-0.04	0.009	-0.036	-0.04	0.012	-0.035	-0.083	-0.017	-0.063	-0.087	-0.02	-0.066
	[0.0566]	[0.0565]	[0.0564]	[0.0586]	[0.0589]	[0.0585]	[0.0563]	[0.0572]	[0.0554]	[0.0567]	[0.0582]	[0.0557]
Firm Characteristics												
ln_globalFirmSales	0.007	0.005	0.007	0.008	0.006	0.008	0.023	0.021	0.02	0.025	0.022	0.021
	[0.0189]	[0.0188]	[0.0189]	[0.0195]	[0.0194]	[0.0195]	[0.0180]	[0.0178]	[0.0178]	[0.0183]	[0.0181]	[0.0181]
Time Since Risk Onset												
sequence	0.017***	0.016***	0.017***	0.017***	0.016***	0.017***	0.033***	0.032***	0.028***	0.034***	0.033***	0.028***
	[0.0032]	[0.0032]	[0.0032]	[0.0035]	[0.0035]	[0.0035]	[0.0032]	[0.0032]	[0.0033]	[0.0034]	[0.0033]	[0.0034]
ln_sequenceSq	-0.339***	-0.335***	-0.339***	-0.350***	-0.345***	-0.350***	-0.414***	-0.410***	-0.399***	-0.424***	-0.419***	-0.407***
	[0.0339]	[0.0340]	[0.0339]	[0.0363]	[0.0363]	[0.0363]	[0.0333]	[0.0333]	[0.0336]	[0.0348]	[0.0347]	[0.0352]
Year Dummies	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Number of observations	19698	19698	19698	19698	19698	19698	19698	19698	19698	19698	19698	19698
Log Likelihood	-2218.21	-2221.42	-2218.47	-2220.04	-2223.32	-2220.28	-2326.57	-2332.77	-2306.01	-2327.9	-2334.26	-2307.48
chi2	737.92	736.01	749.44	681.63	681.78	687.45	418.16	406.76	447.5	380.01	371.24	413.37
p value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Akaike Info Criteria	4530.422	4536.85	4534.93	4534.08	4540.65	4538.56	4731.13	4743.53	4694.02	4733.79	4746.53	4696.95
Bayesian Info Criteria	4901.17	4907.59	4921.46	4904.83	4911.4	4925.08	5038.77	5051.17	5017.44	5041.44	5054.17	5020.37

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets).
Duration dependence is captured by sequence and ln_sequence, which correspond to months since risk onset and the log of squared months since risk onset, i.e. t + ln (t *t) . Year, ATC1 and Country Dummies not reported

Table D.5 Non-parametric Duration Dependence: Coefficients for Base Case Cloglog and Logit Estimates for First Generic Launch (Molecules with First Launch after 1993)

Coefficient Estimates	*With Calendar Year Dummies*						*No Calendar Year Dummies*					
	CLOGLOG			LOGIT			CLOGLOG			LOGIT		
	1	2	3	1	2	3	1	2	3	1	2	3
Expected Generic Price												
LMAvgExpPg	0.052	0.063		0.055*	0.067		0.074**	0.141**		0.076**	0.146**	
	[0.0267]	[0.0413]		[0.0282]	[0.0435]		[0.0256]	[0.0438]		[0.0265]	[0.0452]	
LMAvg_Pb			0.051			0.054			0.073**			0.074**
			[0.0266]			[0.0281]			[0.0248]			[0.0257]
medRatioPgPb			0.199			0.318			-1.743*			-1.835*
			[0.6895]			[0.7224]			[0.7777]			[0.8011]
Expected Market Size												
ExpMarketSizeUSD	0.091**			0.097**			0.187***			0.194***		
	[0.0341]			[0.0365]			[0.0369]			[0.0378]		
ExpMarketSizeSU		0.022			0.022			0.082*			0.086*	
		[0.0305]			[0.0331]			[0.0323]			[0.0334]	
LMAvg_USD_molCtr_			0.087*			0.093*			0.136***			0.142***
			[0.0341]			[0.0366]			[0.0351]			[0.0360]
avgGenShare_USD_			0.001			-0.002			0.095***			0.097***
			[0.0123]			[0.0127]			[0.0110]			[0.0113]
Competition												
NumGenFirmMed	-1.779*	-1.818*	-1.791*	-1.597*	-1.627*	-1.638*	5.761***	5.904***	4.683***	5.905***	6.065***	4.855***
	[0.7671]	[0.7688]	[0.7651]	[0.7990]	[0.8017]	[0.7978]	[0.7922]	[0.7943]	[0.7097]	[0.8117]	[0.8145]	[0.7295]
Molecule Characteristics												
ln_lag_yrs	0.071	0.065	0.071	0.074	0.067	0.073	0.015	0.004	0.023	0.017	0.005	0.025
	[0.0372]	[0.0371]	[0.0372]	[0.0390]	[0.0388]	[0.0390]	[0.0353]	[0.0348]	[0.0349]	[0.0363]	[0.0357]	[0.0361]

ln_MolGlobalUSDAnnual_	0.029	0.082*	0.033	0.036	0.093*	0.04	0.002	0.082*	0.022	0.005	0.087*	0.026
	[0.0385]	[0.0368]	[0.0385]	[0.0404]	[0.0386]	[0.0404]	[0.0395]	[0.0375]	[0.0380]	[0.0400]	[0.0379]	[0.0385]
Firm Characteristics												
ln_globalFirmSales	0.005	0.004	0.005	0.006	0.005	0.006	0.015	0.013	0.011	0.016	0.014	0.012
	[0.0145]	[0.0145]	[0.0145]	[0.0150]	[0.0150]	[0.0150]	[0.0136]	[0.0135]	[0.0131]	[0.0139]	[0.0138]	[0.0134]
Year Dummies	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Monthly Period Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Model Stats												
Number of observations	41104	41104	41104	41104	41104	41104	41104	41104	41104	41104	41104	41104
Log Likelihood	-3302.54	-3306.22	-3302.93	-3294.88	-3298.66	-3295.2	-3505.01	-3516.33	-3465.35	-3503.12	-3514.59	-3463.26
chi2	14057.04	14280.89	14313.13	12763.67	12976.81	12988.19	17497.36	18261.92	18189.47	16603.75	17342.02	17238.23
p value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Akaike Info Criteria	6927.08	6934.44	6931.86	6911.76	6919.31	6916.4	7316.02	7338.65	7240.7	7312.23	7335.19	7236.52
Bayesian Info Criteria	8315.52	8322.88	8337.55	8300.2	8307.75	8322.09	8635.47	8658.1	8577.4	8631.68	8654.64	8573.22

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets).
Duration dependence is captured by sequence and ln_sequence, which correspond to months since risk onset and the log of squared months since risk onset, i.e. $t + \ln(t * t)$. Year, ATC1 and Country Dummies not reported

D.2.2 Robustness Checks

D.2.2.1 Impact of Regulation

Table D.6 Robustness Check: Parametric Duration Dependence, Coefficient Estimates for Regulation (with calendar year dummies)

Variables	1 cloglog	1 logit	2 cloglog	2 logit	3 cloglog	3 logit	4 cloglog	4 logit	5 cloglog	5 logit	6 cloglog	6 logit	7 cloglog	7 logit
Regulation														
LMAvgExpPg	0.150***	0.146***					0.150***	0.146***	0.129**	0.124**	0.146***	0.141**		
	[0.0410]	[0.0429]					[0.0410]	[0.0430]	[0.0430]	[0.0451]	[0.0425]	[0.0447]		
L3ln_ExpPg			0.139***	0.135**										
			[0.0419]	[0.0439]										
ln_ExpPg					0.146***	0.141***								
					[0.0407]	[0.0426]								
L3ln_Pb													0.141***	0.136**
													[0.0418]	[0.0437]
medRatioPgPb					-0.291	0.016							-0.067	0.233
					[0.9626]	[1.0066]							[0.9588]	[1.0032]
RPS							0.161	0.198						
							[0.2421]	[0.2496]						
GenSubst									0.43	0.409				
									[0.3548]	[0.3695]				
LMAvgExpPgxlnT											0.012	0.013		
											[0.0177]	[0.0196]		
Controls														
Market Size														
ExpMarketSizeUSD	0.132*	0.147**	0.127*	0.143*	0.130*	0.145**	0.131*	0.146**	0.122*	0.137*	0.129*	0.145**	0.129*	0.143*
	[0.0534]	[0.0561]	[0.0529]	[0.0556]	[0.0532]	[0.0558]	[0.0533]	[0.0560]	[0.0543]	[0.0569]	[0.0534]	[0.0560]	[0.0527]	[0.0555]
Competition														
norm_IHHatc4_gen	0.647***	0.682***	0.644***	0.679***	0.646***	0.681***	0.647***	0.683***	0.650***	0.683***	0.646***	0.682***	0.645***	0.679***
	[0.0491]	[0.0535]	[0.0491]	[0.0534]	[0.0493]	[0.0535]	[0.0491]	[0.0534]	[0.0504]	[0.0544]	[0.0491]	[0.0534]	[0.0492]	[0.0534]

Molecule Charateristics														
ln_MolGlobalUSDAnnual_	-0.064	-0.069	-0.064	-0.07	-0.054	-0.059	-0.062	-0.067	-0.06	-0.065	-0.062	-0.068	-0.064	-0.069
	[0.0634]	[0.0669]	[0.0630]	[0.0664]	[0.0625]	[0.0664]	[0.0632]	[0.0667]	[0.0659]	[0.0693]	[0.0632]	[0.0667]	[0.0631]	[0.0665]
ln_lag_yrs	0.054	0.077	0.05	0.073	0.047	0.068	0.053	0.076	0.037	0.058	0.056	0.079	0.05	0.072
	[0.0711]	[0.0758]	[0.0709]	[0.0756]	[0.0709]	[0.0755]	[0.0709]	[0.0756]	[0.0719]	[0.0765]	[0.0710]	[0.0757]	[0.0710]	[0.0758]
Firm Charateristics														
ln_globalFirmSales	-0.003	-0.002	-0.002	-0.002	-0.006	-0.006	-0.002	-0.001	0	0	-0.002	-0.002	-0.002	-0.002
	[0.0221]	[0.0228]	[0.0220]	[0.0228]	[0.0221]	[0.0228]	[0.0221]	[0.0228]	[0.0230]	[0.0237]	[0.0221]	[0.0229]	[0.0220]	[0.0228]
Time Since Risk Onset														
sequence	0.018***	0.018***	0.018***	0.018***	0.018***	0.018***	0.018***	0.019***	0.019***	0.019***	0.019***	0.019***	0.018***	0.018***
	[0.0035]	[0.0037]	[0.0035]	[0.0037]	[0.0035]	[0.0037]	[0.0035]	[0.0037]	[0.0036]	[0.0038]	[0.0035]	[0.0037]	[0.0035]	[0.0037]
ln_sequenceSq	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	0.348***	0.360***	0.345***	0.356***	0.344***	0.355***	0.348***	0.360***	0.357***	0.369***	0.353***	0.364***	0.345***	0.357***
	[0.0346]	[0.0376]	[0.0346]	[0.0375]	[0.0348]	[0.0378]	[0.0345]	[0.0376]	[0.0358]	[0.0389]	[0.0354]	[0.0385]	[0.0345]	[0.0375]
Heterogeneity Controls														
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calendar Year Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Model Stats														
Number of observations	19698	19698	19809	19809	19827	19827	19698	19698	18560	18560	19698	19698	19809	19809
Log Likelihood	-2083.37	-2082.67	-2095.24	-2094.59	-2092.62	-2091.99	-2083.12	-2082.32	-1955.74	-1955.23	-2083.01	-2082.36	-2095.04	-2094.47
chi2	798.35	668	790.37	662.33	799.72	671.3	803.27	671.83	776.35	644.57	802.81	670.53	795.13	666.84
p value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0	0
Akaike Info Criteria	4260.73	4259.34	4284.49	4283.18	4281.25	4279.98	4262.23	4260.64	4005.48	4004.47	4262.02	4260.73	4286.08	4284.93
Bayesian Info Criteria	4631.48	4630.09	4655.5	4654.2	4660.2	4658.93	4640.87	4639.27	4373.44	4372.42	4640.65	4639.36	4664.98	4663.84

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets).
Duration dependence is captured by sequence and ln_sequence, which correspond to months since risk onset and the log of squared months since risk onset, i.e. $t + \ln(t * t)$. Year, ATC1 and Country Dummies not reported

Table D.7 Robustness Check: Parametric Duration Dependence, Coefficient Estimates for Regulation (no calendar year dummies)

Variables	1 cloglog	1 logit	2 cloglog	2 logit	3 cloglog	3 logit	4 cloglog	4 logit	5 cloglog	5 logit	6 cloglog	6 logit	7 cloglog	7 logit
Regulation														
LMAvgExpPg	0.154***	0.156***					0.153***	0.156***	0.126**	0.126**	0.151***	0.152***		
	[0.0405]	[0.0419]					[0.0400]	[0.0416]	[0.0422]	[0.0437]	[0.0418]	[0.0430]		
L3ln_ExpPg			0.146***	0.148***										
			[0.0416]	[0.0430]										
ln_ExpPg					0.156***	0.158***								
					[0.0401]	[0.0413]								
L3ln_Pb													0.154***	0.155***
													[0.0410]	[0.0423]
medRatioPgPb					-2.181*	-2.180*							-1.950*	-1.949
					[0.9771]	[1.0122]							[0.9764]	[1.0115]
RPS							0.923***	0.971***						
							[0.1981]	[0.2051]						
GenSubst									1.069**	1.106**				
									[0.3255]	[0.3402]				
LMAvgExpPgxlnT											0.02	0.018		
											[0.0162]	[0.0174]		
Controls														
Market Size														
ExpMarketSizeUSD	0.253***	0.264***	0.251***	0.261***	0.255***	0.265***	0.234***	0.246***	0.234***	0.242***	0.249***	0.260***	0.253***	0.263***
	[0.0549]	[0.0564]	[0.0546]	[0.0560]	[0.0547]	[0.0562]	[0.0551]	[0.0566]	[0.0559]	[0.0570]	[0.0547]	[0.0563]	[0.0544]	[0.0558]
Competition														
norm_IHHatc4_gen	0.676***	0.700***	0.674***	0.698***	0.677***	0.700***	0.673***	0.700***	0.680***	0.700***	0.676***	0.699***	0.677***	0.699***
	[0.0489]	[0.0523]	[0.0488]	[0.0521]	[0.0496]	[0.0527]	[0.0480]	[0.0515]	[0.0502]	[0.0531]	[0.0488]	[0.0522]	[0.0495]	[0.0526]
Molecule Charateristics														
ln_MolGlobalUSDAnnual_	-0.138*	-0.136*	-0.138*	-0.137*	-0.131*	-0.130*	-0.126*	-0.127*	-0.132*	-0.131	-0.136*	-0.135*	-0.142*	-0.140*
	[0.0627]	[0.0641]	[0.0623]	[0.0637]	[0.0618]	[0.0633]	[0.0619]	[0.0634]	[0.0655]	[0.0668]	[0.0623]	[0.0638]	[0.0628]	[0.0642]

ln_lag_yrs	-0.058	-0.052	-0.062	-0.056	-0.057	-0.052	-0.055	-0.049	-0.069	-0.068	-0.053	-0.048	-0.055	-0.049
	[0.0670]	[0.0691]	[0.0668]	[0.0689]	[0.0677]	[0.0697]	[0.0653]	[0.0675]	[0.0681]	[0.0700]	[0.0668]	[0.0689]	[0.0677]	[0.0697]
Firm Charateristics														
ln_globalFirmSales	0.022	0.022	0.023	0.022	0.017	0.016	0.026	0.025	0.026	0.025	0.021	0.021	0.021	0.02
	[0.0216]	[0.0219]	[0.0215]	[0.0218]	[0.0214]	[0.0216]	[0.0213]	[0.0216]	[0.0227]	[0.0229]	[0.0216]	[0.0218]	[0.0215]	[0.0217]
Time Since Risk Onset														
sequence	0.040***	0.042***	0.040***	0.041***	0.039***	0.040***	0.038***	0.040***	0.039***	0.041***	0.041***	0.042***	0.039***	0.040***
	[0.0030]	[0.0032]	[0.0030]	[0.0032]	[0.0031]	[0.0033]	[0.0030]	[0.0032]	[0.0031]	[0.0033]	[0.0030]	[0.0032]	[0.0031]	[0.0033]
ln_sequenceSq	- 0.451***	- 0.468***	- 0.449***	- 0.465***	- 0.447***	- 0.461***	- 0.445***	- 0.462***	- 0.460***	- 0.475***	- 0.459***	- 0.474***	- 0.448***	- 0.462***
	[0.0326]	[0.0349]	[0.0326]	[0.0349]	[0.0329]	[0.0353]	[0.0327]	[0.0351]	[0.0335]	[0.0361]	[0.0331]	[0.0356]	[0.0327]	[0.0351]
Heterogeneity Controls														
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calendar Year Dummies	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Model Stats														
Number of observations	19698	19698	19809	19809	19827	19827	19698	19698	18560	18560	19698	19698	19809	19809
Log Likelihood	-2192.41	-2194.79	-2204.73	-2207.18	-2198.9	-2201.53	-2180.4	-2182.83	-2054.59	-2057.69	-2191.37	-2194.08	-2201.42	-2204.11
chi2	617.43	521.4	611.59	517.1	594.59	505	676.05	566.05	596.08	510.45	617.86	518.99	599.22	508.66
p value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0	0
Akaike Info Criteria	4462.82	4467.58	4487.46	4492.37	4477.8	4483.06	4440.79	4445.67	4187.19	4193.38	4462.74	4468.16	4482.83	4488.22
Bayesian Info Criteria	4770.46	4775.23	4795.32	4800.23	4793.59	4798.85	4756.32	4761.2	4492.51	4498.7	4778.27	4783.69	4798.59	4803.97

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets).
Duration dependence is captured by sequence and ln_sequence, which correspond to months since risk onset and the log of squared months since risk onset, i.e. $t + \ln(t * t)$. Year, ATC1 and Country Dummies not reported

Table D.8 Robustness Check: Non-Parametric Time Duration, Coefficient Estimates for Regulation (with calendar year dummies)

Variables	1 cloglog	1 logit	2 cloglog	2 logit	3 cloglog	3 logit	4 cloglog	4 logit	5 cloglog	5 logit	6 cloglog	6 logit	6 cloglog	6 logit
Regulation														
LMAvgExpPg	0.091**	0.090**					0.091**	0.091**	0.085*	0.085*	0.084*	0.088*		
	[0.0317]	[0.0334]					[0.0317]	[0.0334]	[0.0332]	[0.0350]	[0.0373]	[0.0404]		
L3ln_ExpPg			0.088**	0.088**										
			[0.0318]	[0.0335]										
ln_ExpPg					0.088**	0.087**								
					[0.0318]	[0.0334]								
L3ln_Pb													0.089**	0.088**
													[0.0319]	[0.0335]
medRatioPgPb					-0.28	-0.003							-0.123	0.155
					[0.7484]	[0.7888]							[0.7447]	[0.7846]
RPS							0.143	0.134						
							[0.1708]	[0.1755]						
GenSubst									0.571*	0.574*				
									[0.2498]	[0.2543]				
LMAvgExpPgxlnT											0.005	0.001		
											[0.0134]	[0.0150]		
Controls														
Market Size														
ExpMarketSizeUSD	0.103**	0.117**	0.103**	0.117**	0.106**	0.119**	0.103*	0.116**	0.101*	0.114**	0.102*	0.116**	0.104**	0.117**
	[0.0400]	[0.0427]	[0.0398]	[0.0425]	[0.0399]	[0.0427]	[0.0400]	[0.0427]	[0.0405]	[0.0435]	[0.0402]	[0.0428]	[0.0397]	[0.0425]
Competition														
norm_IHHatc4_gen	0.592***	0.630***	0.590***	0.628***	0.592***	0.629***	0.591***	0.630***	0.590***	0.626***	0.591***	0.630***	0.591***	0.628***
	[0.0414]	[0.0451]	[0.0413]	[0.0449]	[0.0414]	[0.0450]	[0.0413]	[0.0450]	[0.0425]	[0.0460]	[0.0413]	[0.0449]	[0.0413]	[0.0449]

Molecule Characteristics														
ln_MolGlobalUSDAnnual_	0.046	0.051	0.045	0.049	0.048	0.051	0.046	0.05	0.051	0.056	0.047	0.051	0.045	0.049
	[0.0435]	[0.0454]	[0.0433]	[0.0452]	[0.0432]	[0.0453]	[0.0435]	[0.0454]	[0.0447]	[0.0466]	[0.0436]	[0.0454]	[0.0433]	[0.0452]
ln_lag_yrs	0.067	0.075	0.068	0.076	0.067	0.074	0.067	0.075	0.064	0.068	0.068	0.075	0.068	0.076
	[0.0463]	[0.0491]	[0.0461]	[0.0489]	[0.0463]	[0.0490]	[0.0462]	[0.0490]	[0.0475]	[0.0502]	[0.0463]	[0.0492]	[0.0462]	[0.0489]
Firm Characteristics														
ln_globalFirmSales	-0.009	-0.008	-0.009	-0.008	-0.011	-0.01	-0.009	-0.007	-0.012	-0.011	-0.009	-0.008	-0.009	-0.008
	[0.0172]	[0.0179]	[0.0172]	[0.0178]	[0.0172]	[0.0178]	[0.0172]	[0.0179]	[0.0176]	[0.0182]	[0.0172]	[0.0178]	[0.0172]	[0.0178]
Heterogeneity Controls														
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Monthly Period Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calendar Year Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Model Stats														
Number of observations	41104	41104	41453	41453	41455	41455	41104	41104	38099	38099	41104	41104	41453	41453
Log Likelihood	-3142.53	-3129.6	-3159.48	-3146.61	-3153.11	-3140.57	-3142.21	-3129.33	-2939.21	-2926.13	-3142.42	-3129.59	-3159.31	-3146.53
chi2	11498.26	10439.78	11466.27	10400.91	11375.21	10351.42	11538.47	10478.01	10815.71	9771.07	11548.44	10476.95	11458.74	10411.68
p value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Akaike Info Criteria	6607.06	6581.19	6640.95	6615.22	6630.22	6605.14	6608.42	6582.67	6200.43	6174.26	6608.83	6583.18	6642.62	6617.05
Bayesian Info Criteria	7995.5	7969.63	8030.76	8005.03	8028.66	8003.58	8005.49	7979.73	7576.65	7550.48	8005.9	7980.25	8041.05	8015.49

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets).
Duration dependence is captured by sequence and ln_sequence, which correspond to months since risk onset and the log of squared months since risk onset, i.e. $t + \ln(t * t)$. Year, ATC1 and Country Dummies not reported

Table D.9 Robustness Check: Non-Parametric Time Duration, Coefficient Estimates for Regulation (no calendar year dummies)

Variables	1 cloglog	1 logit	2 cloglog	2 logit	3 cloglog	3 logit	4 cloglog	4 logit	5 cloglog	5 logit	6 cloglog	6 logit	7 cloglog	7 logit
Regulation														
LMAvgExpPg	0.108***	0.113***					0.113***	0.118***	0.101**	0.104**	0.112***	0.122***		
	[0.0314]	[0.0324]					[0.0310]	[0.0321]	[0.0325]	[0.0336]	[0.0335]	[0.0348]		
L3ln_ExpPg			0.107***	0.112***										
			[0.0315]	[0.0325]										
ln_ExpPg					0.108***	0.112***								
					[0.0315]	[0.0325]								
L3ln_Pb													0.112***	0.115***
													[0.0314]	[0.0324]
medRatioPgPb					- 2.746***	- 2.798***							-2.566**	-2.612**
					[0.7879]	[0.8213]							[0.7869]	[0.8208]
RPS							0.844***	0.853***						
							[0.1427]	[0.1462]						
GenSubst									1.251***	1.294***				
									[0.2413]	[0.2483]				
LMAvgExpPgxlnT											-0.002	-0.007		
											[0.0131]	[0.0138]		
Controls														
Market Size														
ExpMarketSizeUSD	0.219***	0.227***	0.220***	0.228***	0.217***	0.226***	0.215***	0.223***	0.202***	0.207***	0.218***	0.227***	0.215***	0.223***
	[0.0423]	[0.0434]	[0.0423]	[0.0433]	[0.0424]	[0.0435]	[0.0424]	[0.0434]	[0.0425]	[0.0436]	[0.0423]	[0.0434]	[0.0422]	[0.0433]
Competition														
norm_IHHatc4_gen	0.609***	0.639***	0.608***	0.636***	0.612***	0.640***	0.605***	0.633***	0.607***	0.633***	0.610***	0.640***	0.610***	0.638***
	[0.0418]	[0.0447]	[0.0417]	[0.0446]	[0.0421]	[0.0449]	[0.0413]	[0.0443]	[0.0432]	[0.0456]	[0.0416]	[0.0445]	[0.0420]	[0.0448]

Molecule Characteristics														
ln_MolGlobalUSDAnnual_	0.022	0.03	0.02	0.028	0.027	0.035	0.012	0.021	0.036	0.046	0.022	0.03	0.024	0.032
	[0.0446]	[0.0451]	[0.0445]	[0.0450]	[0.0444]	[0.0448]	[0.0440]	[0.0445]	[0.0457]	[0.0463]	[0.0446]	[0.0451]	[0.0447]	[0.0452]
ln_lag_yrs	0	0	0.001	0.001	0.002	0.002	0.005	0.004	-0.001	-0.006	-0.001	-0.002	0.004	0.004
	[0.0429]	[0.0443]	[0.0428]	[0.0442]	[0.0432]	[0.0447]	[0.0424]	[0.0438]	[0.0440]	[0.0455]	[0.0428]	[0.0443]	[0.0432]	[0.0446]
Firm Characteristics														
ln_globalFirmSales	0.005	0.005	0.005	0.005	0.001	0.002	0.007	0.007	0.004	0.003	0.005	0.005	0.003	0.004
	[0.0163]	[0.0166]	[0.0163]	[0.0166]	[0.0161]	[0.0165]	[0.0163]	[0.0167]	[0.0166]	[0.0170]	[0.0162]	[0.0165]	[0.0161]	[0.0165]
Heterogeneity Controls														
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Monthly Period Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calendar Year Dummies	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Model Stats														
Number of observations	41104	41104	41453	41453	41455	41455	41104	41104	38099	38099	41104	41104	41453	41453
Log Likelihood	-3353.62	-3349.23	-3370.97	-3366.71	-3357.45	-3353.53	-3338.36	-3334.76	-3125.8	-3122.08	-3353.59	-3349.06	-3363.98	-3359.98
chi2	12061.1	11452.3	11997.6	11399.6	11899.4	11291.4	12339.8	11714.9	11570.5	10946.7	12069.6	11455.4	11963.5	11348.3
p value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Akaike Info Criteria	7013.24	7004.47	7047.93	7039.43	7022.89	7015.06	6984.73	6977.51	6557.59	6550.15	7015.18	7006.11	7035.96	7027.96
Bayesian Info Criteria	8332.69	8323.92	8368.68	8360.17	8352.28	8344.44	8312.8	8305.59	7865.43	7857.99	8343.25	8334.19	8365.33	8357.34

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets).
Duration dependence is captured by sequence and ln_sequence, which correspond to months since risk onset and the log of squared months since risk onset, i.e. t + ln (t *t) . Year, ATC1 and Country Dummies not reported

Table D.10 Impact of Expected Generic Prices and Time Interaction

	Cloglog 1	Cloglog 1 (no year dummies)	Cloglog 2	Cloglog 2 (no year dummies)
	b/se/p	b/se/p	b/se/p	b/se/p
L3ln_ExpPg	0.087	0.09		
	[0.0579]	[0.0535]		
	(0.132)	(0.092)		
L3ln_ExpPgxT	0.019	0.021		
	[0.0125]	[0.0115]		
	(0.136)	(0.071)		
LMAvgExpPg			0.088	0.097
			[0.0590]	[0.0533]
			(0.134)	(0.070)
LMAvgExpPgxT			0.002	0.002
			[0.0010]	[0.0010]
			(0.087)	(0.068)
ExpMarketSizeUSD	0.118*	0.241***	0.121*	0.243***
	[0.0529]	[0.0544]	[0.0534]	[0.0548]
	(0.026)	(0.000)	(0.024)	(0.000)
norm_IHHatc4_gen	0.644***	0.675***	0.646***	0.677***
	[0.0491]	[0.0487]	[0.0492]	[0.0489]
	(0.000)	(0.000)	(0.000)	(0.000)
ln_lag_yrs	0.058	-0.051	0.062	-0.049
	[0.0700]	[0.0660]	[0.0703]	[0.0662]
	(0.410)	(0.437)	(0.381)	(0.456)
ln_MolGlobalUSDAnnual_	-0.06	-0.134*	-0.06	-0.135*
	[0.0624]	[0.0619]	[0.0628]	[0.0622]
	(0.337)	(0.030)	(0.342)	(0.030)
ln_globalFirmSales	-0.003	0.02	-0.003	0.02
	[0.0220]	[0.0215]	[0.0221]	[0.0215]
	(0.881)	(0.360)	(0.875)	(0.355)
sequence	0.019***	0.041***	0.019***	0.041***
	[0.0035]	[0.0030]	[0.0035]	[0.0030]
	(0.000)	(0.000)	(0.000)	(0.000)
ln_sequenceSq	-0.354***	-0.459***	-0.357***	-0.461***
	[0.0351]	[0.0330]	[0.0350]	[0.0331]
	(0.000)	(0.000)	(0.000)	(0.000)
Country Dummies	Yes	Yes	Yes	Yes
ATC1 Dummies	Yes	Yes	Yes	Yes
Calendar Year Dummies	Yes	No	Yes	No
N	19809	19809	19698	19698
ll	-2093.45	-2202.42	-2081.17	-2190.19
chi2	803.04	612.52	811.06	619.3
aic	4282.9	4484.84	4258.35	4460.38
bic	4661.81	4800.6	4636.98	4775.91

Note: *p<0.05, **p < 0.01, ***p<0.001.
Standard errors in brackets and p-value in parantheses.
Estimated by complementary log log regression

D.2.2.2 Impact of Market Size

Table D.11 Robustness Check: Parametric Duration Dependence, Coefficient Estimates for Market Size (with calendar year dummies)

Variables	1 cloglog	1 logit	2 cloglog	2 logit	3 cloglog	3 logit	4 cloglog	4 logit	5 cloglog	5 logit	6 cloglog	6 logit
Market Size												
ExpMarketSizeUSD	0.127*	0.143*										
	[0.0529]	[0.0556]										
ExpMarketSizeSU			0.06	0.071								
			[0.0493]	[0.0520]								
LMAvg_USD_molCtr_					0.123*	0.140*						
					[0.0534]	[0.0562]						
LMAvg_SU_molCtr_							0.054	0.066				
							[0.0496]	[0.0524]				
L3ln_USD_moleculeCtry_i									0.103*	0.116*		
									[0.0514]	[0.0541]		
L3ln_SU_moleculeCtry_i											0.044	0.053
											[0.0473]	[0.0499]
ExpMSizeUSDxlnT												
Controls												
Expected Generic Price												
L3ln_ExpPg	0.139***	0.135**	0.188**	0.194**	0.138***	0.134**	0.181*	0.189*	0.157***	0.154***	0.190**	0.197**
	[0.0419]	[0.0439]	[0.0712]	[0.0742]	[0.0420]	[0.0440]	[0.0715]	[0.0746]	[0.0416]	[0.0436]	[0.0688]	[0.0717]
Competition												
norm_IHHatc4_gen	0.644***	0.679***	0.646***	0.679***	0.645***	0.680***	0.646***	0.679***	0.649***	0.684***	0.649***	0.683***
	[0.0491]	[0.0534]	[0.0493]	[0.0534]	[0.0491]	[0.0534]	[0.0493]	[0.0534]	[0.0484]	[0.0527]	[0.0486]	[0.0527]
Molecule Characteristics												
ln_MolGlobalUSDAnnual_	-0.064	-0.07	-0.011	-0.013	-0.061	-0.067	-0.006	-0.009	-0.036	-0.039	0.01	0.01
	[0.0630]	[0.0664]	[0.0612]	[0.0644]	[0.0632]	[0.0666]	[0.0614]	[0.0646]	[0.0614]	[0.0647]	[0.0595]	[0.0626]
ln_lag_yrs	0.05	0.073	0.038	0.058	0.049	0.072	0.036	0.057	0.036	0.057	0.025	0.044
	[0.0709]	[0.0756]	[0.0712]	[0.0757]	[0.0710]	[0.0757]	[0.0713]	[0.0758]	[0.0690]	[0.0732]	[0.0693]	[0.0734]

Firm Characteristics												
ln_globalFirmSales	-0.002	-0.002	-0.003	-0.003	-0.002	-0.002	-0.003	-0.003	-0.002	-0.002	-0.003	-0.002
	[0.0220]	[0.0228]	[0.0220]	[0.0227]	[0.0220]	[0.0228]	[0.0220]	[0.0227]	[0.0214]	[0.0222]	[0.0214]	[0.0222]
Time since risk onset												
sequence	0.018***	0.018***	0.017***	0.017***	0.018***	0.018***	0.017***	0.017***	0.019***	0.020***	0.019***	0.019***
	[0.0035]	[0.0037]	[0.0035]	[0.0038]	[0.0035]	[0.0037]	[0.0035]	[0.0038]	[0.0034]	[0.0037]	[0.0035]	[0.0037]
ln_sequenceSq	-	-	-	-	-	-	-	-	-	-	-	-
	0.345***	0.356***	0.341***	0.352***	0.345***	0.356***	0.341***	0.352***	0.363***	0.377***	0.359***	0.373***
	[0.0346]	[0.0375]	[0.0346]	[0.0376]	[0.0346]	[0.0375]	[0.0346]	[0.0376]	[0.0338]	[0.0368]	[0.0338]	[0.0368]
Heterogeneity Controls												
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calendar Year Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Model Stats												
Number of observations	19809	19809	19809	19809	19809	19809	19809	19809	20708	20708	20708	20708
Log Likelihood	-2095.24	-2094.59	-2098.68	-2098.37	-2095.58	-2094.86	-2098.91	-2098.59	-2149.67	-2149.19	-2152.4	-2152.2
chi2	790.37	662.33	791.14	663.76	788.55	660.11	790.85	663.23	851	715.06	851.5	715.81
p value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Akaike Info Criteria	4284.487	4283.184	4291.356	4290.748	4285.166	4283.73	4291.828	4291.181	4395.339	4394.377	4400.794	4400.41
Bayesian Info Criteria	4655.5	4654.2	4662.37	4661.76	4656.18	4654.74	4662.84	4662.19	4776.38	4775.41	4781.83	4781.45

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets).
Duration dependence is captured by sequence and ln_sequence, which correspond to months since risk onset and the log of squared months since risk onset, i.e. $t + \ln(t * t)$. Year, ATC1 and Country Dummies not reported

Table D.12 Robustness Check: Parametric Duration Dependence, Coefficient Estimates for Market Size (no calendar year dummies)

Variables	1 cloglog	1 logit	2 cloglog	2 logit	3 cloglog	3 logit	4 cloglog	4 logit	5 cloglog	5 logit	6 cloglog	6 logit
Market Size												
ExpMarketSizeUSD	0.251*** [0.0546]	0.261*** [0.0560]										
ExpMarketSizeSU			0.165** [0.0513]	0.172** [0.0527]								
LMAvg_USD_molCtr_					0.220*** [0.0546]	0.231*** [0.0562]						
LMAvg_SU_molCtr_							0.135** [0.0511]	0.141** [0.0525]				
L3ln_USD_moleculeCtry_i									0.191*** [0.0533]	0.200*** [0.0551]		
L3ln_SU_moleculeCtry_i											0.115* [0.0493]	0.120* [0.0508]
ExpMSizeUSDxlnT												
Controls												
Expected Generic Price												
L3ln_ExpPg	0.146*** [0.0416]	0.148*** [0.0430]	0.301*** [0.0714]	0.309*** [0.0733]	0.143*** [0.0418]	0.146*** [0.0431]	0.269*** [0.0714]	0.276*** [0.0733]	0.156*** [0.0417]	0.159*** [0.0432]	0.262*** [0.0689]	0.270*** [0.0709]
Competition												
norm_IHHatc4_gen	0.674*** [0.0488]	0.698*** [0.0521]	0.677*** [0.0490]	0.699*** [0.0521]	0.675*** [0.0488]	0.699*** [0.0521]	0.677*** [0.0490]	0.699*** [0.0520]	0.676*** [0.0483]	0.700*** [0.0515]	0.677*** [0.0484]	0.700*** [0.0515]
Molecule Characteristics												

ln_MolGlobalUSDAnnual_	-0.138*	-0.137*	-0.064	-0.06	-0.112	-0.111	-0.039	-0.035	-0.07	-0.068	-0.006	-0.001
	[0.0623]	[0.0637]	[0.0617]	[0.0632]	[0.0621]	[0.0635]	[0.0613]	[0.0628]	[0.0596]	[0.0614]	[0.0585]	[0.0603]
ln_lag_yrs	-0.062	-0.056	-0.078	-0.074	-0.072	-0.067	-0.09	-0.086	-0.084	-0.08	-0.101	-0.098
	[0.0668]	[0.0689]	[0.0670]	[0.0690]	[0.0667]	[0.0689]	[0.0668]	[0.0689]	[0.0658]	[0.0680]	[0.0658]	[0.0680]
Firm Characteristics												
ln_globalFirmSales	0.023	0.022	0.019	0.019	0.022	0.022	0.019	0.019	0.019	0.018	0.017	0.016
	[0.0215]	[0.0218]	[0.0215]	[0.0218]	[0.0215]	[0.0218]	[0.0215]	[0.0217]	[0.0213]	[0.0217]	[0.0214]	[0.0217]
Time since risk onset												
sequence	0.040***	0.041***	0.039***	0.041***	0.040***	0.042***	0.039***	0.041***	0.042***	0.044***	0.041***	0.043***
	[0.0030]	[0.0032]	[0.0030]	[0.0032]	[0.0030]	[0.0032]	[0.0030]	[0.0032]	[0.0029]	[0.0031]	[0.0029]	[0.0031]
ln_sequenceSq	-0.449***	-0.465***	-0.445***	-0.460***	-0.450***	-0.466***	-0.446***	-0.461***	-0.462***	-0.479***	-0.458***	-0.473***
	[0.0326]	[0.0349]	[0.0325]	[0.0347]	[0.0325]	[0.0348]	[0.0324]	[0.0347]	[0.0321]	[0.0344]	[0.0320]	[0.0343]
Heterogeneity Controls												
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calendar Year Dummies	No	No	No	No	No	No	No	No	No	No	No	No
Model Stats												
Number of observations	19809	19809	19809	19809	19809	19809	19809	19809	20708	20708	20708	20708
Log Likelihood	-2204.73	-2207.18	-2213.07	-2215.73	-2208.6	-2211.04	-2215.93	-2218.58	-2265.12	-2267.88	-2271.66	-2274.6
chi2	611.59	517.1	597.26	505.58	606.18	513	593.88	503.68	651.26	548.81	642.73	541.88
p value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Akaike Info Criteria	4487.463	4492.37	4504.144	4509.465	4495.198	4500.08	4509.86	4515.152	4608.24	4613.765	4621.327	4627.195
Bayesian Info Criteria	4795.32	4800.23	4812.01	4817.33	4803.06	4807.94	4817.72	4823.01	4917.83	4923.36	4930.92	4936.79

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets).
Duration dependence is captured by sequence and ln_sequence, which correspond to months since risk onset and the log of squared months since risk onset, i.e. $t + \ln(t * t)$. Year, ATC1 and Country Dummies not reported

Table D.13 Robustness Check: Non-Parametric Time Duration, Coefficient Estimates for Market Size (with calendar year dummies)

Variables	1 cloglog	1 logit	2 cloglog	2 logit	3 cloglog	3 logit	4 cloglog	4 logit	5 cloglog	5 logit	6 cloglog	6 logit
Market Size												
ExpMarketSizeUSD	0.103** [0.0398]	0.117** [0.0425]										
ExpMarketSizeSU			0.016 [0.0346]	0.023 [0.0375]								
LMAvg_USD_molCtr_					0.100* [0.0400]	0.114** [0.0428]						
LMAvg_SU_molCtr_							0.011 [0.0347]	0.018 [0.0376]				
L3ln_USD_moleculeCtry_i									0.093* [0.0389]	0.105* [0.0416]		
L3ln_SU_moleculeCtry_i											0.014 [0.0332]	0.02 [0.0359]
ExpMSizeUSDxlnT												
Controls												
Expected Generic Price												
L3ln_ExpPg	0.088** [0.0318]	0.088** [0.0335]	0.092 [0.0478]	0.098 [0.0502]	0.088** [0.0318]	0.087** [0.0335]	0.086 [0.0479]	0.093 [0.0502]	0.096** [0.0312]	0.096** [0.0329]	0.099* [0.0461]	0.104* [0.0485]
Competition												
norm_IHHatc4_gen	0.590** * [0.0413]	0.628** * [0.0449]	0.589** * [0.0415]	0.625** * [0.0450]	0.590** * [0.0413]	0.628** * [0.0450]	0.589** * [0.0415]	0.625** * [0.0450]	0.591** * [0.0406]	0.629** * [0.0442]	0.590** * [0.0408]	0.626** * [0.0442]
Molecule Characteristics												
ln_MolGlobalUSDAnnual_	0.045 [0.0433]	0.049 [0.0452]	0.112** [0.0410]	0.122** [0.0429]	0.048 [0.0435]	0.052 [0.0453]	0.116** [0.0411]	0.126** [0.0430]	0.05 [0.0430]	0.056 [0.0449]	0.112** [0.0404]	0.123** [0.0423]

ln_lag_yrs	0.068	0.076	0.061	0.067	0.068	0.076	0.06	0.066	0.07	0.077	0.064	0.069
	[0.0461]	[0.0489]	[0.0462]	[0.0489]	[0.0461]	[0.0489]	[0.0462]	[0.0490]	[0.0451]	[0.0478]	[0.0453]	[0.0479]
Firm Characteristics												
ln_globalFirmSales	-0.009	-0.008	-0.01	-0.009	-0.009	-0.008	-0.01	-0.009	-0.007	-0.005	-0.008	-0.006
	[0.0172]	[0.0178]	[0.0173]	[0.0179]	[0.0172]	[0.0178]	[0.0173]	[0.0179]	[0.0170]	[0.0176]	[0.0171]	[0.0177]
Heterogeneity Controls												
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Monthly Period Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calendar Year Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Model Stats												
Number of observations	41453	41453	41453	41453	41453	41453	41453	41453	45020	45020	45020	45020
Log Likelihood	-3159.48	-3146.61	-3164.34	-3152.08	-3159.88	-3146.96	-3164.42	-3152.17	-3252.8	-3238.29	-3257.11	-3243.13
chi2	11466.27	10400.91	11638.76	10579.51	11486.46	10416.48	11650.34	10591.44	11921.29	10838.04	12078.23	11002.3
p value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Akaike Info Criteria	6640.953	6615.224	6650.673	6626.158	6641.765	6615.924	6650.835	6626.349	6829.602	6800.579	6838.227	6810.256
Bayesian Info Criteria	8030.76	8005.03	8040.48	8015.96	8031.57	8005.73	8040.64	8016.15	8241.41	8212.39	8250.03	8222.06

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets).
Duration dependence is captured by sequence and ln_sequence, which correspond to months since risk onset and the log of squared months since risk onset, i.e. t + ln (t *t) . Year, ATC1 and Country Dummies not reported

Table D.14 Robustness Check: Non-Parametric Time Duration, Coefficient Estimates for Market Size (no calendar year dummies)

Variables	1 cloglog	1 logit	2 cloglog	2 logit	3 cloglog	3 logit	4 cloglog	4 logit	5 cloglog	5 logit	6 cloglog	6 logit
Market Size												
ExpMarketSizeUSD	0.220***	0.228***										
	[0.0423]	[0.0433]										
ExpMarketSizeSU			0.092*	0.094*								
			[0.0357]	[0.0367]								
LMAvg_USD_molCtr_					0.190***	0.197***						
					[0.0418]	[0.0429]						
LMAvg_SU_molCtr_							0.063	0.065				
							[0.0354]	[0.0363]				
L3ln_USD_moleculeCtry_i									0.182***	0.189***		
									[0.0412]	[0.0425]		
L3ln_SU_moleculeCtry_i											0.062	0.063
											[0.0344]	[0.0354]
ExpMSizeUSDxlnT												
Controls												
Expected Generic Price												
L3ln_ExpPg	0.107***	0.112***	0.180***	0.187***	0.104***	0.108***	0.151**	0.156**	0.107***	0.111***	0.153**	0.159**
	[0.0315]	[0.0325]	[0.0491]	[0.0505]	[0.0314]	[0.0324]	[0.0486]	[0.0501]	[0.0312]	[0.0323]	[0.0473]	[0.0489]
Competition												
norm_IHHatc4_gen	0.608***	0.636***	0.605***	0.634***	0.608***	0.637***	0.606***	0.634***	0.605***	0.634***	0.603***	0.632***
	[0.0417]	[0.0446]	[0.0421]	[0.0448]	[0.0417]	[0.0446]	[0.0421]	[0.0447]	[0.0412]	[0.0440]	[0.0414]	[0.0440]
Molecule Characteristics												

ln_MolGlobalUSDAnnual_	0.02	0.028	0.120**	0.132**	0.044	0.053	0.142***	0.155***	0.054	0.063	0.148***	0.162***
	[0.0445]	[0.0450]	[0.0419]	[0.0423]	[0.0443]	[0.0448]	[0.0417]	[0.0421]	[0.0440]	[0.0447]	[0.0413]	[0.0418]
ln_lag_yrs	0.001	0.001	-0.015	-0.018	-0.003	-0.004	-0.019	-0.023	-0.004	-0.005	-0.019	-0.023
	[0.0428]	[0.0442]	[0.0427]	[0.0440]	[0.0427]	[0.0440]	[0.0426]	[0.0439]	[0.0423]	[0.0437]	[0.0421]	[0.0435]
Firm Characteristics												
ln_globalFirmSales	0.005	0.005	0.005	0.005	0.005	0.005	0.004	0.005	0.005	0.006	0.005	0.005
	[0.0163]	[0.0166]	[0.0162]	[0.0166]	[0.0162]	[0.0166]	[0.0162]	[0.0166]	[0.0162]	[0.0166]	[0.0162]	[0.0166]
Heterogeneity Controls												
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Monthly Period Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calendar Year Dummies	No	No	No	No	No	No	No	No	No	No	No	No
Model Stats												
Number of observations	41453	41453	41453	41453	41453	41453	41453	41453	45020	45020	45020	45020
Log Likelihood	-3370.97	-3366.71	-3387.33	-3383.17	-3376.4	-3372.14	-3389.76	-3385.59	-3481.99	-3477.31	-3495.22	-3490.59
chi2	11997.61	11399.58	12557.03	11930.62	12122.94	11514.74	12655.63	12020.45	12069.71	11461.32	12571.75	11944.98
p value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Akaike Info Criteria	7047.933	7039.427	7080.662	7072.349	7058.797	7050.289	7085.522	7077.187	7269.98	7260.628	7296.448	7287.179
Bayesian Info Criteria	8368.68	8360.17	8401.41	8393.09	8379.54	8371.03	8406.27	8397.93	8603.35	8594	8629.82	8620.55

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets).
Duration dependence is captured by sequence and ln_sequence, which correspond to months since risk onset and the log of squared months since risk onset, i.e. $t + \ln(t * t)$. Year, ATC1 and Country Dummies not reported

D.2.2.3 Impact of Competition

Table D.15 Robustness Check: Parametric Duration Dependence, Coefficient Estimates for Competition (with calendar year dummies)

Variables	1 cloglog	1 logit	2 cloglog	2 logit	3 cloglog	3 logit	4 cloglog	4 logit	5 cloglog	5 logit
Competition										
norm_IHHatc4_gen	0.645*** [0.0491]	0.680*** [0.0534]								
NumbMolCtryAtc4_			0.003 [0.0074]	0.004 [0.0075]						
NumbMolCtryRETAtc4_					0.004 [0.0077]	0.005 [0.0078]				
NumGenFirmMed							-1.652 [0.9857]	-1.528 [1.0172]	-1.314 [1.9361]	-0.869 [2.0172]
firmSqMed									-0.106 [0.5114]	-0.207 [0.5349]
Controls										
Expected Generic Price										
L3ln_ExpPg	0.138*** [0.0420]	0.134** [0.0440]	0.080* [0.0382]	0.080* [0.0397]	0.080* [0.0384]	0.080* [0.0398]	0.080* [0.0374]	0.079* [0.0388]	0.080* [0.0374]	0.079* [0.0387]
Expected Market Size										
*LMAvg_USD_molCtr_*	0.123* [0.0534]	0.140* [0.0562]	0.112* [0.0455]	0.120* [0.0473]	0.112* [0.0455]	0.120* [0.0473]	0.113* [0.0449]	0.120* [0.0466]	0.113* [0.0449]	0.120* [0.0467]
Molecule Characteristics										
ln_MolGlobalUSDAnnual_	-0.061 [0.0632]	-0.067 [0.0666]	-0.036 [0.0563]	-0.036 [0.0583]	-0.036 [0.0563]	-0.036 [0.0583]	-0.038 [0.0562]	-0.037 [0.0583]	-0.038 [0.0562]	-0.038 [0.0583]
ln_lag_yrs	0.049 [0.0710]	0.072 [0.0757]	0.122* [0.0620]	0.128* [0.0640]	0.122* [0.0620]	0.128* [0.0640]	0.121* [0.0618]	0.127* [0.0638]	0.122* [0.0618]	0.128* [0.0637]
Firm Characteristics										
ln_globalFirmSales	-0.002 [0.0220]	-0.002 [0.0228]	0.008 [0.0190]	0.009 [0.0195]	0.008 [0.0190]	0.009 [0.0195]	0.007 [0.0189]	0.008 [0.0194]	0.007 [0.0189]	0.008 [0.0195]
Time Since Risk Onset										

sequence	0.018***	0.018***	0.016***	0.016***	0.016***	0.016***	0.016***	0.017***	0.016***	0.017***
	[0.0035]	[0.0037]	[0.0032]	[0.0035]	[0.0032]	[0.0035]	[0.0032]	[0.0035]	[0.0032]	[0.0035]
ln_sequenceSq	-	-	-	-	-	-	-	-	-	-
	0.345***	0.356***	0.331***	0.342***	0.331***	0.343***	0.335***	0.346***	0.335***	0.346***
	[0.0346]	[0.0375]	[0.0340]	[0.0364]	[0.0340]	[0.0364]	[0.0339]	[0.0363]	[0.0340]	[0.0363]
Heterogeneity										
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calendar Year Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Model Stats										
Number of observations	19809	19809	19809	19809	19809	19809	19809	19809	19809	19809
Log Likelihood	-2095.58	-2094.86	-2231.52	-2232.97	-2231.5	-2232.96	-2230.23	-2231.99	-2230.21	-2231.93
chi2	788.55	660.11	719.56	659.22	719.68	659.48	723.32	668.24	721.62	664.89
p value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Akaike Info Criteria	4285.17	4283.73	4557.04	4559.93	4557.01	4559.91	4554.46	4557.98	4556.43	4559.86
Bayesian Info Criteria	4656.18	4654.74	4928.05	4930.94	4928.02	4930.92	4925.48	4928.99	4935.34	4938.76

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets).
Duration dependence is captured by sequence and ln_sequence, which correspond to months since risk onset and the log of squared months since risk onset, i.e. $t + \ln(t * t)$. Year, ATC1 and Country Dummies not reported

Table D.16 Robustness Check: Parametric Duration Dependence, Coefficient Estimates for Competition (no calendar year dummies)

Variables	1 cloglog	1 logit	2 cloglog	2 logit	3 cloglog	3 logit	4 cloglog	4 logit	5 cloglog	5 logit
Competition										
norm_IHHatc4_gen	0.675*** [0.0488]	0.699*** [0.0521]								
NumbMolCtryAtc4_			-0.003 [0.0073]	-0.003 [0.0074]						
NumbMolCtryRETAtc4_					-0.001 [0.0075]	-0.001 [0.0076]				
NumGenFirmMed							6.295*** [0.9550]	6.443*** [0.9714]	10.800*** [1.9957]	11.110*** [2.0638]
firmSqMed									-1.553* [0.6067]	-1.603** [0.6214]
Controls										
Expected Generic Price										
L3ln_ExpPg	0.143*** [0.0418]	0.146*** [0.0431]	0.099** [0.0380]	0.101** [0.0387]	0.101** [0.0382]	0.102** [0.0388]	0.089* [0.0367]	0.090* [0.0376]	0.089* [0.0365]	0.089* [0.0373]
Expected Market Size										
*LMAvg_USD_molCtr_*	0.220*** [0.0546]	0.231*** [0.0562]	0.196*** [0.0476]	0.204*** [0.0482]	0.197*** [0.0476]	0.205*** [0.0483]	0.166*** [0.0466]	0.175*** [0.0476]	0.164*** [0.0466]	0.172*** [0.0476]
Molecule Characteristics										
ln_MolGlobalUSDAnnual_	-0.112 [0.0621]	-0.111 [0.0635]	-0.068 [0.0572]	-0.073 [0.0576]	-0.069 [0.0572]	-0.073 [0.0576]	-0.06 [0.0556]	-0.064 [0.0561]	-0.06 [0.0555]	-0.065 [0.0560]
ln_lag_yrs	-0.072 [0.0667]	-0.067 [0.0689]	-0.027 [0.0592]	-0.026 [0.0603]	-0.027 [0.0591]	-0.025 [0.0602]	0.014 [0.0595]	0.015 [0.0608]	0.024 [0.0591]	0.026 [0.0604]
Firm Characteristics										
ln_globalFirmSales	0.022 [0.0215]	0.022 [0.0218]	0.03 [0.0181]	0.031 [0.0183]	0.03 [0.0181]	0.031 [0.0183]	0.024 [0.0179]	0.025 [0.0182]	0.024 [0.0179]	0.025 [0.0182]

Time Since Risk Onset										
sequence	0.040***	0.042***	0.040***	0.041***	0.040***	0.041***	0.032***	0.033***	0.032***	0.033***
	[0.0030]	[0.0032]	[0.0029]	[0.0031]	[0.0029]	[0.0031]	[0.0032]	[0.0034]	[0.0032]	[0.0034]
ln_sequenceSq	-	-	-	-	-	-	-	-	-0.411***	-0.421***
	0.450***	0.466***	0.449***	0.457***	0.449***	0.457***	0.411***	0.420***		
	[0.0325]	[0.0348]	[0.0321]	[0.0334]	[0.0321]	[0.0334]	[0.0332]	[0.0347]	[0.0333]	[0.0348]
Heterogeneity										
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calendar Year Dummies	No	No	No	No	No	No	No	No	No	No
Model Stats										
Number of observations	19809	19809	19809	19809	19809	19809	19809	19809	19809	19809
Log Likelihood	-2208.6	-2211.04	-2369.12	-2370.47	-2369.18	-2370.53	-2340.88	-2342.28	-2337.28	-2338.64
chi2	606.18	513	344.69	322.29	344.69	322.18	407.39	371.58	409.98	371.69
p value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Akaike Info Criteria	4495.2	4500.08	4816.23	4818.94	4816.36	4819.06	4759.76	4762.55	4754.55	4757.28
Bayesian Info Criteria	4803.06	4807.94	5124.09	5126.8	5124.22	5126.92	5067.62	5070.42	5070.31	5073.04

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets).
Duration dependence is captured by sequence and ln_sequence, which correspond to months since risk onset and the log of squared months since risk onset, i.e. $t + \ln(t * t)$. Year, ATC1 and Country Dummies not reported

Table D.17 Robustness Check: Non-Parametric Time Duration, Coefficient Estimates for Competition (with calendar year dummies)

Variables	1 cloglog	1 logit	2 cloglog	2 logit	3 cloglog	3 logit	4 cloglog	4 logit	5 cloglog	5 logit
Competition										
norm_IHHatc4_gen	0.590***	0.628***								
	[0.0413]	[0.0450]								
NumbMolCtryAtc4_			0	0.001						
			[0.0059]	[0.0061]						
NumbMolCtryRETAtc4_					0	0.001				
					[0.0061]	[0.0064]				
NumGenFirmMed							-1.754*	-1.571*	-0.849	-0.34
							[0.7634]	[0.7953]	[1.5672]	[1.6388]
firmSqMed									-0.289	-0.397
									[0.4353]	[0.4611]
Controls										
Expected Generic Price										
L3ln_ExpPg	0.088**	0.087**	0.048	0.052	0.048	0.052	0.048	0.052	0.048	0.052
	[0.0318]	[0.0335]	[0.0274]	[0.0290]	[0.0275]	[0.0291]	[0.0268]	[0.0284]	[0.0269]	[0.0284]
Expected Market Size										
LMAvg_USD_molCtr_	0.100*	0.114**	0.088*	0.093*	0.088*	0.093*	0.086*	0.092*	0.086*	0.092*
	[0.0400]	[0.0428]	[0.0345]	[0.0370]	[0.0345]	[0.0370]	[0.0340]	[0.0364]	[0.0340]	[0.0365]
Molecule Characteristics										
ln_MolGlobalUSDAnnual_	0.048	0.052	0.031	0.039	0.031	0.039	0.033	0.039	0.033	0.04
	[0.0435]	[0.0453]	[0.0388]	[0.0407]	[0.0388]	[0.0407]	[0.0383]	[0.0403]	[0.0384]	[0.0404]
ln_lag_yrs	0.068	0.076	0.073	0.076	0.073	0.076	0.071	0.074	0.071	0.074
	[0.0461]	[0.0489]	[0.0372]	[0.0390]	[0.0372]	[0.0390]	[0.0371]	[0.0389]	[0.0371]	[0.0389]
Firm Characteristics										
ln_globalFirmSales	-0.009	-0.008	0.005	0.006	0.005	0.006	0.005	0.006	0.005	0.006
	[0.0172]	[0.0178]	[0.0146]	[0.0151]	[0.0146]	[0.0151]	[0.0145]	[0.0151]	[0.0146]	[0.0152]

Heterogeneity										
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Monthly Period Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calendar Year Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Model Stats										
Number of observations	41453	41453	41453	41453	41453	41453	41453	41453	41453	41453
Log Likelihood	-3159.88	-3146.96	-3322.12	-3313.77	-3322.12	-3313.78	-3319.66	-3311.95	-3319.48	-3311.64
chi2	11486.46	10416.48	14404.27	13003	14404.07	13001.55	14082.64	12772	14163.2	12852.67
p value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Akaike Info Criteria	6641.77	6615.92	6966.25	6949.55	6966.25	6949.56	6961.31	6945.89	6962.95	6947.28
Bayesian Info Criteria	8031.57	8005.73	8356.05	8339.35	8356.05	8339.37	8351.12	8335.7	8361.39	8345.72

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets).
Duration dependence is captured by sequence and ln_sequence, which correspond to months since risk onset and the log of squared months since risk onset, i.e. $t + \ln(t * t)$. Year, ATC1 and Country Dummies not reported

Table D.18 Robustness Check: Non-Parametric Time Duration, Coefficient Estimates for Competition (no calendar year dummies)

Variables	1 cloglog	1 logit	2 cloglog	2 logit	3 cloglog	3 logit	4 cloglog	4 logit	5 cloglog	5 logit
Competition										
norm_IHHatc4_gen	0.608***	0.637***								
	[0.0417]	[0.0446]								
NumbMolCtryAtc4_			-0.002	-0.001						
			[0.0062]	[0.0063]						
NumbMolCtryRETAtc4_					-0.001	0				
					[0.0064]	[0.0066]				
NumGenFirmMed							5.875***	6.022***	10.480***	10.804***
							[0.7945]	[0.8137]	[1.7792]	[1.8136]
firmSqMed									-1.627**	-1.686**
									[0.5656]	[0.5698]
Controls										
Expected Generic Price										
L3ln_ExpPg	0.104***	0.108***	0.070**	0.072**	0.071**	0.073**	0.069**	0.071**	0.067**	0.070**
	[0.0314]	[0.0324]	[0.0261]	[0.0270]	[0.0262]	[0.0270]	[0.0257]	[0.0266]	[0.0257]	[0.0265]
Expected Market Size										
LMAvg_USD_molCtr_	0.190***	0.197***	0.176***	0.183***	0.176***	0.183***	0.159***	0.165***	0.154***	0.160***
	[0.0418]	[0.0429]	[0.0364]	[0.0370]	[0.0364]	[0.0370]	[0.0360]	[0.0369]	[0.0357]	[0.0366]
Molecule Characteristics										
ln_MolGlobalUSDAnnual_	0.044	0.053	0.027	0.029	0.027	0.03	0.023	0.026	0.023	0.026
	[0.0443]	[0.0448]	[0.0395]	[0.0400]	[0.0396]	[0.0400]	[0.0390]	[0.0395]	[0.0389]	[0.0394]

ln_lag_yrs	-0.003	-0.004	-0.004	-0.003	-0.003	-0.003	0.012	0.013	0.014	0.016
	[0.0427]	[0.0440]	[0.0346]	[0.0355]	[0.0346]	[0.0355]	[0.0352]	[0.0361]	[0.0350]	[0.0360]
Firm Characteristics										
ln_globalFirmSales	0.005	0.005	0.018	0.019	0.018	0.019	0.014	0.016	0.015	0.016
	[0.0162]	[0.0166]	[0.0134]	[0.0137]	[0.0134]	[0.0137]	[0.0135]	[0.0138]	[0.0136]	[0.0139]
Heterogeneity										
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Monthly Period Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calendar Year Dummies	No	No	No	No	No	No	No	No	No	No
Model Stats										
Number of observations	41453	41453	41453	41453	41453	41453	41453	41453	41453	41453
Log Likelihood	-3376.4	-3372.14	-3562.78	-3560.75	-3562.8	-3560.77	-3526.15	-3524.35	-3520.93	-3518.98
chi2	12122.94	11514.74	16452.16	15625.57	16465.89	15637.74	17544.2	16656.66	17748.89	16839.8
p value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Akaike Info Criteria	7058.8	7050.29	7431.56	7427.5	7431.6	7427.53	7358.31	7354.7	7349.86	7345.96
Bayesian Info Criteria	8379.54	8371.03	8752.3	8748.25	8752.35	8748.28	8679.05	8675.44	8679.23	8675.33

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets).
Duration dependence is captured by sequence and ln_sequence, which correspond to months since risk onset and the log of squared months since risk onset, i.e. t + ln (t *t) . Year, ATC1 and Country Dummies not reported

D.2.2.4 Impact of Molecule Characteristics

Table D.19 Robustness Check: Parametric Duration Dependence, Coefficient Estimates for Molecule Characteristics (with calendar year dummies)

Variables	cloglog 1	logit 1	cloglog 2	logit 2	cloglog 3	logit 3
Molecule						
MolGlobalReach	-0.009	-0.013				
	[0.0407]	[0.0431]				
ln_MolGlobalUSDAnnual_			-0.061	-0.067		
			[0.0632]	[0.0666]		
ln_MolGlobalUSDMedian_					-0.116	-0.133
					[0.0667]	[0.0707]
ln_lag_yrs	0.051	0.071	0.049	0.072	0.037	0.058
	[0.0707]	[0.0746]	[0.0710]	[0.0757]	[0.0710]	[0.0758]
Controls						
Expected Generic Price						
L3ln_ExpPg	0.138**	0.134**	0.138***	0.134**	0.139***	0.134**
	[0.0427]	[0.0447]	[0.0420]	[0.0440]	[0.0416]	[0.0437]
Expected Market Size						
LMAvg_USD_molCtr_	0.092*	0.107*	0.123*	0.140*	0.152**	0.173**
	[0.0435]	[0.0457]	[0.0534]	[0.0562]	[0.0549]	[0.0575]
Competition						
norm_IHHatc4_gen	0.642***	0.677***	0.645***	0.680***	0.646***	0.682***
	[0.0490]	[0.0533]	[0.0491]	[0.0534]	[0.0492]	[0.0536]

Firm Characteristics						
ln_globalFirmSales	-0.005	-0.005	-0.002	-0.002	0.001	0.002
	[0.0217]	[0.0224]	[0.0220]	[0.0228]	[0.0218]	[0.0226]
sequence	0.018***	0.018***	0.018***	0.018***	0.018***	0.018***
	[0.0035]	[0.0038]	[0.0035]	[0.0037]	[0.0035]	[0.0038]
ln_sequenceSq	-0.347***	-0.359***	-0.345***	-0.356***	-0.344***	-0.355***
	[0.0346]	[0.0375]	[0.0346]	[0.0375]	[0.0346]	[0.0376]
Heterogeneity						
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes
Calendar Year Dummies	Yes	Yes	Yes	Yes	Yes	Yes
Model Stats						
Number of observations	19809	19809	19809	19809	19809	19809
Log Likelihood	-2096.28	-2095.6	-2095.58	-2094.86	-2093.88	-2092.8
chi2	785.49	656.23	788.55	660.11	779.78	651.61
p value	0.000	0.000	0.000	0.000	0.000	0.000
Akaike Info Criteria	4286.56	4285.2	4285.17	4283.73	4281.76	4279.61
Bayesian Info Criteria	4657.57	4656.21	4656.18	4654.74	4652.78	4650.62

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets). Duration dependence is captured by sequence and ln_sequence, which correspond to months since risk onset and the log of squared months since risk onset, i.e. $t + \ln(t * t)$. Year, ATC1 and Country Dummies not reported

Table D.20 Robustness Check: Parametric Duration Dependence, Coefficient Estimates for Molecule Characteristics (no calendar year dummies)

Variables	cloglog 1	logit 1	cloglog 2	logit 2	cloglog 3	logit 3
Molecule						
MolGlobalReach	-0.062	-0.061				
	[0.0383]	[0.0393]				
ln_MolGlobalUSDAnnual_			-0.112	-0.111		
			[0.0621]	[0.0635]		
ln_MolGlobalUSDMedian_					-0.241***	-0.244***
					[0.0618]	[0.0636]
ln_lag_yrs	-0.094	-0.088	-0.072	-0.067	-0.089	-0.082
	[0.0670]	[0.0691]	[0.0667]	[0.0689]	[0.0664]	[0.0688]
Controls						
Expected Generic Price						
L3ln_ExpPg	0.139**	0.141**	0.143***	0.146***	0.140***	0.141***
	[0.0427]	[0.0441]	[0.0418]	[0.0431]	[0.0413]	[0.0426]
Expected Market Size						
LMAvg_USD_molCtr_	0.177***	0.187***	0.220***	0.231***	0.289***	0.302***
	[0.0431]	[0.0443]	[0.0546]	[0.0562]	[0.0542]	[0.0557]
Competition						
norm_IHHatc4_gen	0.670***	0.694***	0.675***	0.699***	0.682***	0.705***
	[0.0490]	[0.0522]	[0.0488]	[0.0521]	[0.0486]	[0.0520]
Firm Characteristics						

ln_globalFirmSales	0.02	0.02	0.022	0.022	0.029	0.029
	[0.0214]	[0.0216]	[0.0215]	[0.0218]	[0.0214]	[0.0217]
sequence	0.041***	0.042***	0.040***	0.042***	0.040***	0.041***
	[0.0030]	[0.0032]	[0.0030]	[0.0032]	[0.0030]	[0.0032]
ln_sequenceSq	-0.452***	-0.468***	-0.450***	-0.466***	-0.448***	-0.464***
	[0.0323]	[0.0345]	[0.0325]	[0.0348]	[0.0324]	[0.0348]
Heterogeneity						
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes
Calendar Year Dummies	No	No	No	No	No	No
Model Stats						
Number of observations	19809	19809	19809	19809	19809	19809
Log Likelihood	-2208.57	-2211.01	-2208.6	-2211.04	-2200.35	-2203.1
chi2	610.25	518.75	606.18	513	617.93	520.73
p value	0.000	0.000	0.000	0.000	0.000	0.000
Akaike Info Criteria	4495.15	4500.01	4495.2	4500.08	4478.7	4484.2
Bayesian Info Criteria	4803.01	4807.87	4803.06	4807.94	4786.57	4792.06

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets). Duration dependence is captured by sequence and ln_sequence, which correspond to months since risk onset and the log of squared months since risk onset, i.e. $t + \ln(t * t)$. Year, ATC1 and Country Dummies not reported

Table D.21 Robustness Check: Non-Parametric Time Duration, Coefficient Estimates for Molecule Characteristics (with calendar year dummies)

Variables	cloglog 1	logit 1	cloglog 2	logit 2	cloglog 3	logit 3
Molecule Characteristics						
MolGlobalReach	-0.007	-0.005				
	[0.0262]	[0.0271]				
ln_MolGlobalUSDAnnual_			0.048	0.052		
			[0.0435]	[0.0453]		
ln_MolGlobalUSDMedian_					0.025	0.024
					[0.0447]	[0.0468]
ln_lag_yrs	0.059	0.068	0.068	0.076	0.065	0.073
	[0.0468]	[0.0495]	[0.0461]	[0.0489]	[0.0461]	[0.0488]
Controls						
Expected Generic Price						
L3ln_ExpPg	0.090**	0.090**	0.088**	0.087**	0.089**	0.089**
	[0.0316]	[0.0333]	[0.0318]	[0.0335]	[0.0318]	[0.0334]
Expected Market Size						
LMAvg_USD_molCtr_	0.131***	0.147***	0.100*	0.114**	0.114**	0.132**
	[0.0312]	[0.0328]	[0.0400]	[0.0428]	[0.0402]	[0.0428]
Competition						
norm_IHHatc4_gen	0.589***	0.627***	0.590***	0.628***	0.590***	0.628***
	[0.0412]	[0.0449]	[0.0413]	[0.0450]	[0.0412]	[0.0449]
Firm Characteristics						

ln_globalFirmSales	-0.008 [0.0171]	-0.006 [0.0177]	-0.009 [0.0172]	-0.008 [0.0178]	-0.009 [0.0171]	-0.007 [0.0178]
Heterogeneity						
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes
Monthly Period Dummies	Yes	Yes	Yes	Yes	Yes	Yes
Calendar Year Dummies	Yes	Yes	Yes	Yes	Yes	Yes
Model Stats						
Number of observations	41453	41453	41453	41453	41453	41453
Log Likelihood	-3160.65	-3147.81	-3159.88	-3146.96	-3160.47	-3147.66
chi2	11328.87	10279.03	11486.46	10416.48	11472.95	10393.23
p value	0.000	0.000	0.000	0.000	0.000	0.000
Akaike Info Criteria	6643.29	6617.62	6641.77	6615.92	6642.95	6617.31
Bayesian Info Criteria	8033.1	8007.42	8031.57	8005.73	8032.75	8007.12

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets). Duration dependence is captured by sequence and ln_sequence, which correspond to months since risk onset and the log of squared months since risk onset, i.e. $t + \ln(t * t)$. Year, ATC1 and Country Dummies not reported

Table D.22 Robustness Check: Non-Parametric Time Duration, Coefficient Estimates for Molecule Characteristics (no calendar year dummies)

Variables	cloglog 1	logit 1	cloglog 2	logit 2	cloglog 3	logit 3
Molecule Characteristics						
MolGlobalReach	-0.028	-0.025				
	[0.0281]	[0.0284]				
ln_MolGlobalUSDAnnual_			0.044	0.053		
			[0.0443]	[0.0448]		
ln_MolGlobalUSDMedian_					-0.026	-0.02
					[0.0432]	[0.0442]
ln_lag_yrs	-0.015	-0.015	-0.003	-0.004	-0.01	-0.01
	[0.0434]	[0.0448]	[0.0427]	[0.0440]	[0.0426]	[0.0440]
Controls						
Expected Generic Price						
L3ln_ExpPg	0.109***	0.114***	0.104***	0.108***	0.110***	0.114***
	[0.0310]	[0.0320]	[0.0314]	[0.0324]	[0.0311]	[0.0322]
Expected Market Size						
LMAvg_USD_molCtr_	0.229***	0.240***	0.190***	0.197***	0.234***	0.243***
	[0.0322]	[0.0330]	[0.0418]	[0.0429]	[0.0413]	[0.0425]
Competition						
norm_IHHatc4_gen	0.606***	0.634***	0.608***	0.637***	0.607***	0.635***
	[0.0418]	[0.0446]	[0.0417]	[0.0446]	[0.0417]	[0.0446]
Firm Characteristics						

ln_globalFirmSales	0.006 [0.0161]	0.007 [0.0165]	0.005 [0.0162]	0.005 [0.0166]	0.006 [0.0161]	0.007 [0.0165]
Heterogeneity						
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes
Monthly Period Dummies	Yes	Yes	Yes	Yes	Yes	Yes
Calendar Year Dummies	No	No	No	No	No	No
Model Stats						
Number of observations	41453	41453	41453	41453	41453	41453
Log Likelihood	-3376.18	-3372.41	-3376.4	-3372.14	-3376.81	-3372.92
chi2	11809.27	11229.76	12122.94	11514.74	11956.61	11372.14
p value	0.000	0.000	0.000	0.000	0.000	0.000
Akaike Info Criteria	7058.37	7050.83	7058.8	7050.29	7059.62	7051.84
Bayesian Info Criteria	8379.11	8371.57	8379.54	8371.03	8380.37	8372.58

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets). Duration dependence is captured by sequence and ln_sequence, which correspond to months since risk onset and the log of squared months since risk onset, i.e. $t + \ln(t * t)$. Year, ATC1 and Country Dummies not reported

Table D.23 Robustness Check for Percent Retail Sales

Variables	*Parametric*				*Non-Parametric*			
	cloglog (with year dummies)	cloglog (no year dummies)	logit (with year dummies)	logit (no year dummies)	cloglog (with year dummies)	cloglog (no year dummies)	logit (with year dummies)	logit (no year dummies)
% Retail Sales of Molecule								
PercRetailUSD_	0.000	0.000	-0.001	0.000	0.005*	0.007**	0.005*	0.008**
	[0.0035]	[0.0037]	[0.0036]	[0.0038]	[0.0024]	[0.0024]	[0.0025]	[0.0024]
Controls								
Expected Generic Price								
L3ln_ExpPg	0.159*	0.191*	0.159*	0.198*	0.161**	0.220***	0.173***	0.236***
	[0.0763]	[0.0797]	[0.0782]	[0.0801]	[0.0498]	[0.0483]	[0.0517]	[0.0494]
Expected Market Size								
LMAvg_USD_molCtr_	0.081	0.129*	0.09	0.138*	0.08	0.127**	0.091*	0.140**
	[0.0580]	[0.0584]	[0.0602]	[0.0598]	[0.0414]	[0.0430]	[0.0436]	[0.0443]
Competition								
norm_IHHatc4_gen	0.724***	0.734***	0.748***	0.758***	0.695***	0.708***	0.734***	0.747***
	[0.0653]	[0.0647]	[0.0688]	[0.0679]	[0.0509]	[0.0506]	[0.0550]	[0.0538]
Firm Characteristics								
ln_globalFirmSales	0.000	0.016	0.000	0.017	0.006	0.02	0.009	0.022
	[0.0305]	[0.0295]	[0.0313]	[0.0298]	[0.0231]	[0.0220]	[0.0237]	[0.0224]
ln_lag_yrs	0.156	0.072	0.17	0.083	0.057	0.016	0.069	0.026
	[0.0889]	[0.0837]	[0.0924]	[0.0858]	[0.0579]	[0.0548]	[0.0604]	[0.0562]

Time since risk onset								
sequence	0.023***	0.042***	0.024***	0.044***				
	[0.0051]	[0.0042]	[0.0053]	[0.0044]				
ln_sequenceSq	-0.348***	-0.425***	-0.364***	-0.443***				
	[0.0508]	[0.0467]	[0.0527]	[0.0484]				
Heterogeneity								
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calendar year Dummies	Yes	No	Yes	No	Yes	No	Yes	No
Monthly period Dummies	No	No	No	No	Yes	Yes	Yes	Yes
Model Stats								
Number of observations	13528	13528	13528	13528	27057	27057	27057	27057
Log Likelihood	-1314.59	-1347.55	-1314.65	-1347.58	-1989.91	-2054.61	-1984.72	-2050.94
chi2	416.89	357.76	369.35	322.64	6936.15	6859.53	6523.45	6504.18
p value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Akaike Info Criteria	2709.19	2761.09	2709.3	2761.17	4261.82	4377.22	4251.43	4369.89
Bayesian Info Criteria	3009.69	3009.01	3009.8	3009.08	5418.83	5476.78	5408.44	5469.45

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets).
Duration dependence is captured by sequence and ln_sequence, which correspond to months since risk onset and the log of squared months since risk onset, i.e. $t + \ln(t * t)$. Year, ATC1 and Country Dummies not reported

D.2.2.5 Impact of Firm Characteristics

Table D.24 Robustness Check: Parametric Duration Dependence, Coefficient Estimates for Firm Characteristics (with calendar year dummies)

Variables	cloglog 1	logit 1	cloglog 2	logit 2	cloglog 3	logit 3	cloglog 4	logit 4
Firm Characteristics								
lnLocalCorpSales	-0.015	-0.014						
	[0.0278]	[0.0297]						
ln_globalFirmSales			-0.002	-0.002				
			[0.0220]	[0.0228]				
CorpGlobalReach					0.006	0.005		
					[0.0088]	[0.0092]		
FirmMolDivAtT_							0	0
							[0.0002]	[0.0002]
Controls								
Expected Generic Prices								
L3ln_ExpPg	0.143***	0.139**	0.138***	0.134**	0.136**	0.133**	0.130**	0.128**
	[0.0433]	[0.0455]	[0.0420]	[0.0440]	[0.0419]	[0.0438]	[0.0424]	[0.0445]
Expected Market Size								
LMAvg_USD_molCtr_	0.124*	0.141*	0.123*	0.140*	0.126*	0.143*	0.113*	0.128*
	[0.0542]	[0.0571]	[0.0534]	[0.0562]	[0.0534]	[0.0563]	[0.0534]	[0.0563]
Competition								
norm_IHHatc4_gen	0.648***	0.683***	0.645***	0.680***	0.647***	0.682***	0.653***	0.689***
	[0.0490]	[0.0533]	[0.0491]	[0.0534]	[0.0486]	[0.0529]	[0.0487]	[0.0529]

Molecule Characteristics								
ln_MolGlobalUSDAnnual_	-0.055	-0.062	-0.061	-0.067	-0.07	-0.076	-0.073	-0.078
	[0.0648]	[0.0683]	[0.0632]	[0.0666]	[0.0617]	[0.0651]	[0.0618]	[0.0647]
ln_lag_yrs	0.053	0.077	0.049	0.072	0.047	0.07	0.025	0.046
	[0.0714]	[0.0762]	[0.0710]	[0.0757]	[0.0712]	[0.0758]	[0.0699]	[0.0747]
Time Since Risk Onset								
sequence	0.018***	0.018***	0.018***	0.018***	0.018***	0.018***	0.017***	0.017***
	[0.0035]	[0.0037]	[0.0035]	[0.0037]	[0.0035]	[0.0037]	[0.0035]	[0.0038]
ln_sequenceSq	-	-	-	-	-	-	-	-
	0.343***	0.355***	0.345***	0.356***	0.344***	0.356***	0.342***	0.353***
	[0.0347]	[0.0377]	[0.0346]	[0.0375]	[0.0345]	[0.0374]	[0.0346]	[0.0376]
Heterogeneity								
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calendar Year Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Model Stats								
Number of observations	19518	19518	19809	19809	20050	20050	20130	20130
Log Likelihood	-2079.68	-2078.93	-2095.58	-2094.86	-2102.48	-2101.82	-2117.8	-2117.14
chi2	780.34	658.03	788.55	660.11	808.33	673.33	802.82	666.74
p value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Akaike Info Criteria	4253.35	4251.86	4285.17	4283.73	4298.96	4297.63	4329.6	4328.28
Bayesian Info Criteria	4623.67	4622.18	4656.18	4654.74	4670.54	4669.21	4701.37	4700.04

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets). Duration dependence is captured by sequence and ln_sequence, which correspond to months since risk onset and the log of squared months since risk onset, i.e. $t + \ln(t * t)$. Year, ATC1 and Country Dummies not reported

Table D.25 Robustness Check: Parametric Duration Dependence, Coefficient Estimates for Firm Characteristics (no calendar year dummies)

Variables	cloglog 1	logit 1	cloglog 2	logit 2	cloglog 3	logit 3	cloglog 4	logit 4
Firm Characteristics								
lnLocalCorpSales	0.063*	0.065*						
	[0.0287]	[0.0298]						
ln_globalFirmSales			0.022	0.022				
			[0.0215]	[0.0218]				
CorpGlobalReach					0.001	0.001		
					[0.0086]	[0.0088]		
FirmMolDivAtT_							0.000*	0.000*
							[0.0002]	[0.0002]
Controls								
Expected Generic Prices								
L3ln_ExpPg	0.146***	0.149***	0.143***	0.146***	0.147***	0.150***	0.143***	0.145***
	[0.0436]	[0.0450]	[0.0418]	[0.0431]	[0.0416]	[0.0430]	[0.0418]	[0.0431]
Expected Market Size								
LMAvg_USD_molCtr_	0.222***	0.232***	0.220***	0.231***	0.219***	0.229***	0.213***	0.223***
	[0.0560]	[0.0577]	[0.0546]	[0.0562]	[0.0545]	[0.0561]	[0.0543]	[0.0559]
Competition								
norm_IHHatc4_gen	0.678***	0.702***	0.675***	0.699***	0.678***	0.702***	0.686***	0.711***
	[0.0487]	[0.0520]	[0.0488]	[0.0521]	[0.0488]	[0.0521]	[0.0484]	[0.0517]

Molecule Characteristics								
ln_MolGlobalUSDAnnual_	-0.131*	-0.130*	-0.112	-0.111	-0.105	-0.104	-0.117	-0.116
	[0.0637]	[0.0651]	[0.0621]	[0.0635]	[0.0610]	[0.0624]	[0.0605]	[0.0617]
ln_lag_yrs	-0.065	-0.059	-0.072	-0.067	-0.071	-0.065	-0.097	-0.092
	[0.0675]	[0.0697]	[0.0667]	[0.0689]	[0.0672]	[0.0694]	[0.0657]	[0.0681]
Time Since Risk Onset								
sequence	0.039***	0.041***	0.040***	0.042***	0.040***	0.042***	0.040***	0.041***
	[0.0030]	[0.0032]	[0.0030]	[0.0032]	[0.0030]	[0.0032]	[0.0030]	[0.0032]
ln_sequenceSq	- 0.445***	- 0.461***	- 0.450***	- 0.466***	-0.450***	- 0.466***	- 0.448***	- 0.464***
	[0.0328]	[0.0350]	[0.0325]	[0.0348]	[0.0324]	[0.0347]	[0.0325]	[0.0348]
Heterogeneity								
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calendar Year Dummies	No	No	No	No	No	No	No	No
Model Stats								
Number of observations	19518	19518	19809	19809	20050	20050	20130	20130
Log Likelihood	-2190.34	-2192.66	-2208.6	-2211.04	-2216.6	-2219.01	-2230.83	-2233.29
chi2	597.01	508.24	606.18	513	613.64	518.9	614.54	521.67
p value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Akaike Info Criteria	4458.67	4463.33	4495.2	4500.08	4511.21	4516.02	4539.66	4544.58
Bayesian Info Criteria	4765.96	4770.61	4803.06	4807.94	4819.54	4824.35	4848.14	4853.07

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets). Duration dependence is captured by sequence and ln_sequence, which correspond to months since risk onset and the log of squared months since risk onset, i.e. $t + \ln(t * t)$. Year, ATC1 and Country Dummies not reported

Table D.26 Robustness Check: Non-Parametric Time Duration, Coefficient Estimates for Firm Characteristics (with calendar year dummies)

Variables	cloglog 1	logit 1	cloglog 2	logit 2	cloglog 3	logit 3	cloglog 4	logit 4
Firm Characteristics								
lnLocalCorpSales	-0.026	-0.024						
	[0.0222]	[0.0240]						
ln_globalFirmSales			-0.009	-0.008				
			[0.0172]	[0.0178]				
CorpGlobalReach					0.001	0.002		
					[0.0068]	[0.0072]		
FirmMolDivAtT_							0	0
							[0.0002]	[0.0002]
Controls								
Expected Generic Price								
L3ln_ExpPg	0.082*	0.081*	0.088**	0.087**	0.084**	0.084*	0.090**	0.091**
	[0.0324]	[0.0342]	[0.0318]	[0.0335]	[0.0318]	[0.0335]	[0.0322]	[0.0340]
Expected Market Size								
LMAvg_USD_molCtr_	0.101*	0.116**	0.100*	0.114**	0.097*	0.111**	0.105**	0.120**
	[0.0401]	[0.0429]	[0.0400]	[0.0428]	[0.0400]	[0.0428]	[0.0403]	[0.0431]
Competition								
norm_IHHatc4_gen	0.598***	0.637***	0.590***	0.628***	0.588***	0.625***	0.595***	0.634***
	[0.0412]	[0.0451]	[0.0413]	[0.0450]	[0.0411]	[0.0447]	[0.0411]	[0.0448]

Molecule Characteristics								
ln_MolGlobalUSDAnnual_	0.053	0.057	0.048	0.052	0.048	0.052	0.037	0.039
	[0.0440]	[0.0460]	[0.0435]	[0.0453]	[0.0432]	[0.0451]	[0.0437]	[0.0455]
ln_lag_yrs	0.074	0.083	0.068	0.076	0.066	0.074	0.064	0.073
	[0.0464]	[0.0493]	[0.0461]	[0.0489]	[0.0461]	[0.0488]	[0.0462]	[0.0489]
Heterogeneity								
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Monthly Period Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calendar Year Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Model Stats								
Number of observations	40874	40874	41453	41453	42088	42088	42058	42058
Log Likelihood	-3134.84	-3121.77	-3159.88	-3146.96	-3179.06	-3166.07	-3192.97	-3179.68
chi2	11498.75	10393.66	11486.46	10416.48	11619.12	10535.08	11631.51	10557.9
p value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Akaike Info Criteria	6591.68	6565.55	6641.77	6615.92	6680.13	6654.13	6707.94	6681.36
Bayesian Info Criteria	7979.22	7953.08	8031.57	8005.73	8072.38	8046.38	8100.08	8073.5

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets).
Duration dependence is captured by sequence and ln_sequence, which correspond to months since risk onset and the log of squared months since risk onset, i.e. $t + \ln(t * t)$. Year, ATC1 and Country Dummies not reported

Table D.27 Robustness Check: Non-Parametric Time Duration, Coefficient Estimates for Firm Characteristics (no calendar year dummies)

Variables	cloglog 1	logit 1	cloglog 2	logit 2	cloglog 3	logit 3	cloglog 4	logit 4
Firm Characteristics								
lnLocalCorpSales	0.042	0.044						
	[0.0228]	[0.0237]						
ln_globalFirmSales			0.005	0.005				
			[0.0162]	[0.0166]				
CorpGlobalReach					-0.006	-0.006		
					[0.0065]	[0.0067]		
FirmMolDivAtT_							0	0
							[0.0001]	[0.0001]
Controls								
Expected Generic Price								
L3ln_ExpPg	0.104**	0.108**	0.104***	0.108***	0.103***	0.108***	0.111***	0.115***
	[0.0321]	[0.0331]	[0.0314]	[0.0324]	[0.0311]	[0.0321]	[0.0312]	[0.0322]
Expected Market Size								
LMAvg_USD_molCtr_	0.189***	0.196***	0.190***	0.197***	0.184***	0.191***	0.196***	0.204***
	[0.0423]	[0.0435]	[0.0418]	[0.0429]	[0.0415]	[0.0426]	[0.0422]	[0.0434]
Competition								
norm_IHHatc4_gen	0.612***	0.642***	0.608***	0.637***	0.609***	0.637***	0.614***	0.643***
	[0.0420]	[0.0450]	[0.0417]	[0.0446]	[0.0415]	[0.0443]	[0.0416]	[0.0445]

Molecule Characteristics								
ln_MolGlobalUSDAnnual_	0.044	0.052	0.044	0.053	0.049	0.059	0.033	0.041
	[0.0452]	[0.0458]	[0.0443]	[0.0448]	[0.0439]	[0.0443]	[0.0446]	[0.0452]
ln_lag_yrs	-0.004	-0.005	-0.003	-0.004	-0.003	-0.004	-0.009	-0.009
	[0.0432]	[0.0445]	[0.0427]	[0.0440]	[0.0427]	[0.0441]	[0.0425]	[0.0438]
Heterogeneity								
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Monthly Period Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calendar Year Dummies	No	No	No	No	No	No	No	No
Model Stats								
Number of observations	40874	40874	41453	41453	42088	42088	42058	42058
Log Likelihood	-3349.43	-3344.94	-3376.4	-3372.14	-3395.61	-3391.48	-3409.2	-3404.71
chi2	11919.14	11315.89	12122.94	11514.74	12190.12	11570.41	12327.55	11731.62
p value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Akaike Info Criteria	7004.87	6995.89	7058.8	7050.29	7097.22	7088.96	7124.4	7115.42
Bayesian Info Criteria	8323.46	8314.48	8379.54	8371.03	8420.29	8412.03	8447.37	8438.38

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets).
Duration dependence is captured by sequence and ln_sequence, which correspond to months since risk onset and the log of squared months since risk onset, i.e. $t + \ln(t * t)$. Year, ATC1 and Country Dummies not reported

D.2.3: Multicollinearity

Table D.28 Variance Inflation Factors with number of generic firms in the market

Variable	*VIF*	*1/VIF*
NumGenFirmMed	244.7	0.0041
country == US	187.5	0.0053
country == GERMANY	102.13	0.0098
country == ITALY	34.07	0.0293
country == UK	14.49	0.0690
country == POLAND	13.04	0.0767
country == SPAIN	11.31	0.0884
country == GREECE	11.19	0.0893
country == JAPAN	10.65	0.0939
country == FRANCE	10.09	0.0991
year == 2003	8.05	0.1242
year == 2002	7.58	0.1319
year == 2004	7.52	0.1330
year == 2001	6.67	0.1500
year == 2005	6.61	0.1514
year == 2006	5.65	0.1770

Variable	*VIF*	*1/VIF*
sequence	5.34	0.1872
country == BELGIUM	5.09	0.1964
year == 2000	4.93	0.2029
ln_sequenceSq	4.22	0.2370
country == CANADA	4.09	0.2443
year == 2007	3.94	0.2535
ExpMarketSizeUSD	3.84	0.2604
country == SWITZERLAND	3.59	0.2788
country == PORTUGAL	3.2	0.3120
country == TURKEY	3.17	0.3154
ATC1 == N	2.88	0.3477
LMAvgExpPg	2.82	0.3552
country == S. AFRICA	2.63	0.3800
ATC1 == L	2.53	0.3946
ln_MolGlobalUSDAnnual_	2.38	0.4204
country == FINLAND	2.36	0.4229

Variable	*VIF*	*1/VIF*
country == SWEDEN	2.22	0.4514
ATC1 == C	2.21	0.4527
ATC1 == M	2.13	0.4690
country == NETHERLANDS	2.01	0.4979
ATC1 == R	1.89	0.5297
ATC1 == J	1.86	0.5370
country == BELGIUM	1.85	0.5394
ATC1 == D	1.6	0.6257
ATC1 == H	1.59	0.6285
ln_globalFirmSales	1.55	0.6435
ATC1 == G	1.55	0.6459
ln_lag_yrs	1.52	0.6584
ATC1 == S	1.2	0.8312
ATC1 == B	1.12	0.8897
Mean VIF	**16.58**	

Command:

```
xi: regress _d LMAvgExpPg ExpMarketSizeUSD NumGenFirmMed ln_MolGlobalUSDAnnual_ ln_lag_yrs ln_globalFirmSales
sequence ln_sequenceSq i.year i.countrynosector i.atc1
estat vif
```

Table D.29 Variance Inflation Factors with Herfindahl Index in ATC4

Variable	*VIF*	*1/VIF*
year == 2003	7.71	0.1297
year == 2004	7.26	0.1377
year == 2002	7.21	0.1386
year == 2005	6.47	0.1545
year == 2001	6.11	0.1636
year == 2006	5.62	0.1781
sequence	5.34	0.1874
year == 2000	4.34	0.2305
ln_sequenceSq	4.21	0.2374
year == 2007	3.94	0.2539
ExpMarketSizeUSD	3.83	0.2608
country == US	3.46	0.2893
ATC1 == N	2.97	0.3362
LMAvgExpPg	2.81	0.3553
country == S. Africa	2.63	0.3803

Variable	*VIF*	*1/VIF*
ATC1 == L	2.61	0.3835
country == CANADA	2.49	0.4013
country == GERMANY	2.4	0.4160
ln_MolGlobalUSDAnnual_	2.38	0.4205
country == SPAIN	2.36	0.4245
country == FINLAND	2.31	0.4332
ATC1 == C	2.22	0.4506
country == PORTUGAL	2.19	0.4571
country == GREECE	2.17	0.4606
country == UK	2.15	0.4645
ATC1 == M	2.14	0.4675
country == AUSTRIA	2.07	0.4823
country == TURKEY	2.06	0.4865
country == FRANCE	2.05	0.4879
country == SWEDEN	2	0.4994

Variable	*VIF*	*1/VIF*
country == JAPAN	1.99	0.5016
country == NETHERLANDS	1.95	0.5117
country == POLAND	1.95	0.5128
ATC1 == J	1.9	0.5271
ATC1 == R	1.89	0.5286
country == ITALY	1.85	0.5402
country == BELGIUM	1.84	0.5448
country == SWITZERLAND	1.79	0.5594
ATC1 == D	1.62	0.6154
ATC1 == H	1.59	0.6271
ln_globalFirmSales	1.56	0.6415
ATC1 == G	1.55	0.6457
ln_lag_yrs	1.52	0.6593
ATC1 == S	1.2	0.8302
norm_IHHatc4_gen	1.2	0.8343
ATC1 == B	1.12	0.8916
Mean VIF	**2.91**	

Command:

xi: regress _d LMAvgExpPg ExpMarketSizeUSD norm_IHHatc4_gen ln_MolGlobalUSDAnnual_ ln_lag_yrs ln_globalFirmSales sequence ln_sequenceSq i.year i.countrynosector i.atc1

estat vif

Table D.30 Parametric Duration Dependence: Coefficients using Herfindahl Index as a proxy for competition

Variables	*with calendar year dummies*						*no calendar year dummies*					
	cloglog 1	cloglog 2	cloglog 3	logit 1	logit 2	logit 3	cloglog 1	cloglog 2	cloglog 3	logit 1	logit 2	logit 3
Expected Generic Price												
LMAvgExpPg	0.150***	0.218**		0.146***	0.226**		0.154***	0.325***		0.156***	0.335***	
	[0.0410]	[0.0725]		[0.0429]	[0.0756]		[0.0405]	[0.0722]		[0.0419]	[0.0742]	
LMAvg_Pb			0.151***			0.146***			0.159***			0.159***
			[0.0409]			[0.0428]			[0.0390]			[0.0402]
medRatioPgPb			-0.005			0.304			-1.391			-1.422
			[0.9584]			[1.0083]			[0.9505]			[0.9865]
Expected Market Size												
ExpMarketSizeUSD	0.132*			0.147**			0.253***			0.264***		
	[0.0534]			[0.0561]			[0.0549]			[0.0564]		
ExpMarketSizeSU		0.077			0.089			0.180***			0.187***	
		[0.0520]			[0.0548]			[0.0534]			[0.0550]	
LMAvg_USD_molCtr_			0.127*			0.144*			0.203***			0.209***
			[0.0537]			[0.0567]			[0.0554]			[0.0567]
avgGenShare_USD_			0.007			0			0.084***			0.088***
			[0.0168]			[0.0175]			[0.0139]			[0.0143]
Competition												
norm_IHHatc4_gen	0.647***	0.648***	0.647***	0.682***	0.683***	0.683***	0.676***	0.679***	0.664***	0.700***	0.702***	0.688***
	[0.0491]	[0.0493]	[0.0493]	[0.0535]	[0.0535]	[0.0536]	[0.0489]	[0.0491]	[0.0498]	[0.0523]	[0.0522]	[0.0529]
Molecule Characteristics												
ln_MolGlobalUSDAnnual_	-0.064	-0.019	-0.059	-0.069	-0.022	-0.066	-0.138*	-0.073	-0.117	-0.136*	-0.069	-0.112
	[0.0634]	[0.0626]	[0.0635]	[0.0669]	[0.0660]	[0.0671]	[0.0627]	[0.0627]	[0.0628]	[0.0641]	[0.0643]	[0.0648]
ln_lag_yrs	0.054	0.046	0.053	0.077	0.067	0.076	-0.058	-0.07	-0.038	-0.052	-0.066	-0.032
	[0.0711]	[0.0714]	[0.0713]	[0.0758]	[0.0759]	[0.0761]	[0.0670]	[0.0673]	[0.0667]	[0.0691]	[0.0694]	[0.0689]

Firm Characteristics												
ln_globalFirmSales	-0.003	-0.004	-0.003	-0.002	-0.004	-0.002	0.022	0.019	0.02	0.022	0.019	0.019
	[0.0221]	[0.0221]	[0.0220]	[0.0228]	[0.0229]	[0.0228]	[0.0216]	[0.0216]	[0.0213]	[0.0219]	[0.0219]	[0.0216]
Time Since Risk Onset												
sequence	0.018***	0.017***	0.018***	0.018***	0.018***	0.018***	0.040***	0.039***	0.034***	0.042***	0.041***	0.035***
	[0.0035]	[0.0035]	[0.0034]	[0.0037]	[0.0038]	[0.0037]	[0.0030]	[0.0030]	[0.0033]	[0.0032]	[0.0032]	[0.0035]
ln_sequenceSq	-	-	-	-	-	-	-	-	-	-	-	-
	0.348***	0.344***	0.348***	0.360***	0.356***	0.360***	0.451***	0.447***	0.431***	0.468***	0.462***	0.445***
	[0.0346]	[0.0346]	[0.0345]	[0.0376]	[0.0376]	[0.0376]	[0.0326]	[0.0325]	[0.0334]	[0.0349]	[0.0349]	[0.0359]
Heterogeneity												
ATC1 Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Country Dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calendar Year Dummies	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Model Stats												
Number of observations	19698	19698	19698	19698	19698	19698	19698	19698	19698	19698	19698	19698
Log Likelihood	-2083.37	-2086.36	-2083.47	-2082.67	-2085.94	-2082.87	-2192.41	-2199.68	-2170.06	-2194.79	-2202.22	-2172.71
chi2	798.35	798.11	817.25	668	669.02	682.63	617.43	604.45	615.58	521.4	510.85	530.79
p value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Akaike Info Criteria	4260.73	4266.72	4264.94	4259.34	4265.87	4263.75	4462.82	4477.37	4422.13	4467.58	4482.45	4427.42
Bayesian Info Criteria	4631.48	4637.47	4651.46	4630.09	4636.62	4650.28	4770.46	4785.01	4745.55	4775.23	4790.09	4750.84

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets). Duration dependence is captured by sequence and ln_sequence, which correspond to months since risk onset and the log of squared months since risk onset, i.e. $t + \ln(t * t)$. Year, ATC1 and Country Dummies not reported

Appendix D.3: Theoretical Appendix

D.3.1 Product Market Competition with Differentiated Goods

Following Singh and Vives (1984), consider N+1 firms, 1 branded producer and N generic entrants, let consumers have the following utility function (Singh and Vives 1984; Häckner 2000; Mestre-Ferrandiz 2003; Cellini, Lambertini et al. 2004; Motta 2004):

$$V = y + U(q_0, q_1, ...q_N)$$

Following the argument in Motta (2004) (see section 8.4, page 562), y is the composite good and consumers maximize V by selecting $\{q_0, q_1, ...q_N, y\}$ subject to the budget constraint (Motta 2004):

$$p_0 q_0 + p_1 q_1 + ... + p_N q_N + p_y y = R$$

The Lagrangian is:

$$L = y + U(q_0, q_1, ...q_N) + \lambda\left[R - \left(p_0 q_0 + p_1 q_1 + ... + p_N q_N + p_y y\right)\right] \quad [1]$$

$$\frac{\partial L}{\partial q_i} = \frac{\partial U(q_0, q_1, ...q_N)}{\partial q_i} - \lambda \cdot p_i = 0, \; i = 0,1,...N$$

$$\frac{\partial L}{\partial y} = 1 - \lambda \cdot p_y = 0,$$

$$\frac{\partial L}{\partial \lambda} = R - p_0 q_0 - p_1 q_1 - .... - p_N q_N - p_y . y$$

By taking the composite good as the numeraire $p_y = 1$ and $\lambda = 1$. The first order condition (FOC) with respect to the differentiated good market becomes:

$$\frac{\partial U(q_0, q_1, ...q_N)}{\partial q_i} = p_i \qquad [2]$$

This FOC can be analyzed independently of the market for the composite good. Motto (2004) specifies that the quasi-linearity in the utility function V justifies a partial equilibrium analysis of the differentiated good market.

Assume the following utility function:

$$U(q_0, q_1, \ldots q_N) = \sum_i \alpha_i q_i - \frac{1}{2}\left[\beta\left(\sum_i q_i^2\right) + 2\gamma \sum_{i \neq j} q_i q_j\right],$$

The FOC given by $\frac{\partial U(q_0, q_1, \ldots q_N)}{\partial q_i} = p_i$ defines the inverse demand equations:

$$p_i = \alpha_i - \beta q_i - \gamma \sum_{j \neq i} q_j \qquad [3]$$

In matrix notation this system of equations can be represented as $\mathbf{p} = \boldsymbol{\alpha} - \mathbf{B}\mathbf{q}$.

where $\mathbf{p}' = [p_0, p_1, \ldots, p_N]$, $\boldsymbol{\alpha}' = [\alpha_0, \alpha_1, \ldots, \alpha_N]$ and $\mathbf{q}' = [q_0, q_1, \ldots, q_N]$

$$\mathbf{B} = \begin{bmatrix} \beta & \gamma & \cdots & & \gamma \\ \gamma & \beta & & & \\ \vdots & & \ddots & & \vdots \\ & & & \beta & \gamma \\ \gamma & \gamma & \cdots & \gamma & \beta \end{bmatrix} = (\beta - \gamma)\mathbf{I} + \gamma \mathbf{O},$$

where $\mathbf{O}$ is a matrix which has entries of 1 for each element and $\mathbf{I}$ is the identity matrix.
Direct demand equations can be calculated from $\mathbf{p} = \boldsymbol{\alpha} - \mathbf{B}\mathbf{q}$ as:

$$\mathbf{q} = \mathbf{B}^{-1}(\boldsymbol{\alpha} - \mathbf{p}), \qquad [4]$$

where $\mathbf{B}^{-1}$, $\mathbf{B}$, $\mathbf{O}$ and $\mathbf{I}$ have a dimension of $(N+1)(N+1)$.

$$\mathbf{B}^{-1} = \frac{1}{\beta - \gamma}\mathbf{I} - \frac{\gamma}{(\beta - \gamma)(\beta + \gamma \cdot N)}\mathbf{O}$$

The inverse of $\mathbf{B}$ can be found as follows:

$$\mathbf{B}\mathbf{B}^{-1} = \mathbf{I}$$

$$\{(\beta - \gamma)\mathbf{I} + \gamma \mathbf{O}\}\left\{\frac{1}{(\beta - \gamma)}\mathbf{I} - x\mathbf{O}\right\} = \mathbf{I}$$

Using $\mathbf{O}^2 = (N+1)\mathbf{O}$

$$(\beta-\gamma)\frac{1}{(\beta-\gamma)}\mathbf{I}^2-(\beta-\gamma)x\mathbf{O}+\gamma\frac{1}{(\beta-\gamma)}\mathbf{O}-\gamma x\mathbf{O}^2=\mathbf{I}$$

$$\mathbf{O}\left\{-(\beta-\gamma)x+\gamma\frac{1}{(\beta-\gamma)}-\gamma x(N+1)\right\}=0$$

$$x(\beta-\gamma+\gamma(N+1))=\gamma\frac{1}{(\beta-\gamma)}$$

$$x=\frac{\gamma}{(\beta-\gamma)(\beta+\gamma\cdot N)}\ \blacksquare$$

The diagonal entries of $\mathbf{B}^{-1}$ are therefore

$\frac{1}{\beta-\gamma}-\frac{\gamma}{(\beta-\gamma)(\beta+\gamma\cdot N)}=\frac{\beta+\gamma\cdot N-\gamma}{(\beta-\gamma)(\beta+\gamma\cdot N)}$, and off-diagonal entries are

$-\frac{\gamma}{(\beta-\gamma)(\beta+\gamma\cdot N)}$.

Using $\mathbf{q}=\mathbf{B}^{-1}(\boldsymbol{\alpha}-\mathbf{p})$, the system of direct demand functions can be written as:

$$q_i=\frac{\beta+\gamma\cdot N-\gamma}{(\beta-\gamma)(\beta+\gamma\cdot N)}(\alpha_i-p_i)-\frac{\gamma}{(\beta-\gamma)(\beta+\gamma\cdot N)}\sum_{k\neq i}(\alpha_k-p_k)\ \text{for}\ i=$$

0,1,...,N

Let $\kappa=\frac{\beta+\gamma\cdot N-\gamma}{(\beta-\gamma)(\beta+\gamma\cdot N)}$, $\kappa>0$ since $\beta>\gamma$.

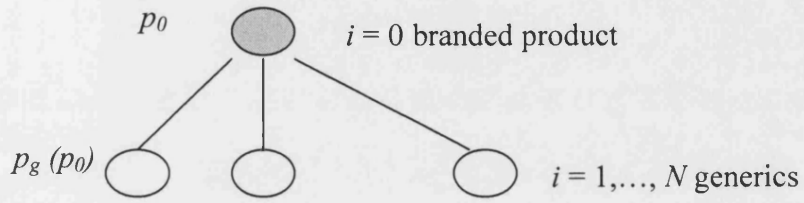
and $\tau=\frac{\gamma}{(\beta-\gamma)(\beta+\gamma\cdot N)}$, $\tau>0$ and $\kappa>\tau$ since $\beta>\gamma>0$.

$$q_i=\left(\kappa\cdot\alpha_i-\tau\sum_{k\neq i}\alpha_k\right)-\kappa\cdot p_i+\tau\sum_{k\neq i}p_k \qquad [5]$$

Note that since $\kappa>\tau$, own-price effect is greater than the cross-price effect.

D.3.2 Equilibrium with a Branded Stackelberg Leader and *N* Generic Entrants

This game analytic problem consists of two stages: in the first stage the branded Stackelberg leader sets the price; in the second stage N identical generic entrants simultaneously determine their equilibrium prices.



The relevant concept is subgame perfect equilibrium (or subgame perfect Nash equilibrium) and the equilibrium is found by "backward induction". First, consider the case where N generic products compete simultaneously in price given the price of the originator product, assuming there are no capacity or quantity constraints. Each generic entrant maximizes its profits given the number of entrants and the branded price. Consider the one-shot optimization problem of generics:

$$\underset{p_i}{Max}\,\Pi_i = q_i(p_i - c_i) = \left(\kappa\cdot\alpha_i - \tau\sum_{k\neq i}\alpha_k - \kappa\cdot p_i + \tau\sum_{k\neq i} p_k\right)(p_i - c_i) - F_i$$

$$\text{FOC: } \frac{\partial\Pi_i}{\partial p_i} = -\kappa(p_i - c_i) + \kappa\cdot\alpha_i - \tau\sum_{k\neq i}\alpha_k - \kappa\cdot p_i + \tau\sum_{k\neq i} p_k = 0,$$

$i \in \{1,\ldots,N\}$

$$\left[\frac{\partial^2\Pi_i}{\partial p_i^2} = -2\kappa < 0,\ \text{FOC is sufficient for optimality}\right]$$

Assume generic entrants are symmetric, i.e. $c_i = c_g$ and $\alpha_i = \alpha_g$, implies demand functions and FOC conditions for generic entrants are symmetric. Therefore, in equilibrium prices will be identical $p_i = p_g$, $i \in \{1,\ldots,N\}$. Plugging in these values into the FOC condition:

$$\left(-2\kappa + \tau\cdot(N-1)\right)\cdot p_g + \kappa\cdot c_g + \kappa\cdot\alpha_g - \tau\left(\alpha_0 + (N-1)\cdot\alpha_g\right) + \tau\cdot p_0 = 0$$

$$p_g(p_0) = \frac{\kappa \cdot c_g + \kappa \cdot \alpha_g - \tau\left(\alpha_0 + (N-1)\cdot \alpha_g\right) + \tau \cdot p_0}{2\kappa - \tau \cdot (N-1)}. \qquad [6]$$

$$\frac{\partial p_g}{\partial p_0} = \frac{\tau}{2\kappa - \tau \cdot (N-1)} > 0 \text{, since } 2\kappa - \tau \cdot (N-1) = \frac{2\beta + \gamma \cdot (N-1)}{(\beta - \gamma)(\beta + \gamma \cdot N)} > 0$$

Plugging in the values for κ, τ, the following reaction function is obtained:

$$p_g(p_0) = \frac{\left(c_g + \alpha_g\right)\left(\beta + \gamma(N-1)\right) - \gamma \cdot \alpha_0 - \gamma \cdot (N-1)\alpha_g + \gamma \cdot p_0}{(\beta - \gamma)(\beta + \gamma N)\left(2\beta + \gamma(N-1)\right)}^{155}, \qquad [7]$$

D.3.2.1 Findings

Finding 1. The generic price level and the branded price are strategic complements, i.e. equilibrium prices of the generic fringe increase as the branded price increases, holding the number of entrants, β and degree of differentiation fixed.

Proof:

For N and γ, β (and hence $\psi = \gamma / \beta$) fixed:

$$\frac{\partial p_g}{\partial p_0} = \frac{\gamma}{(\beta - \gamma)(\beta + \gamma N)\left(2\beta + \gamma(N-1)\right)} > 0. \blacksquare$$

Equilibrium prices are derived assuming there is no price cap for the equilibrium price level of the branded product. If the branded prices are capped and pushed downward, then prices of generics will be pushed down as well and incentives for generic entry will decrease.

$$\frac{\partial^2 p_g^*}{\partial p_0 \partial N} = -\frac{\gamma}{(\beta - \gamma)} \cdot \frac{\left(3\beta\gamma + \gamma^2(2N-1)\right)}{(\beta + \gamma N)^2\left(2\beta + \gamma(N-1)\right)^2} < 0,$$

i.e. as N increases the response of p_g^* to changes in p_0 decreases.

---

[155] $p_g(p_0)$ should satisfy: $p_g(p_0) > 0$ and $p_g(p_0) > c_g$ and $p_g(p_0) > a_g$ since $p_i - \alpha_i = \beta q_i + \gamma \sum_{j \neq i} q_j$

Finding 2. Generic prices decrease in the number of generic entrants if $\beta > \gamma > 0.25$.

Proof:

$$p_g(p_0) = \frac{(c_g + \alpha_g)(\beta + \gamma(N-1)) - \gamma \cdot \alpha_0 - \gamma \cdot (N-1)\alpha_g + \gamma \cdot p_0}{(\beta - \gamma)(\beta + \gamma N)(2\beta + \gamma(N-1))}$$

$$\frac{\partial p_g}{\partial N} = -\frac{\gamma}{(\beta - \gamma)(\beta + \gamma N)(2\beta + \gamma(N-1))}\{(3\beta + \gamma(2N-1))p_g - c_g\} < 0$$

$\Leftrightarrow (3\beta + \gamma(2N-1))p_g - c_g > 0$ given the fact that $p_g \geq c_g$ in equilibrium (i.e. positive mark-up over marginal cost).

Note: $3\beta + \gamma(2N-1) > 3\gamma + \gamma(2N-1) = 2\gamma(N+1)$ since $\beta > \gamma$ by assumption.

$(3\beta + \gamma(2N-1))p_g - c_g > 2\gamma(N+1)p_g - c_g > 4\gamma p_g - c_g$

(Last inequality obtained by setting $N = 1$).

A lower bound on γ can be defined by using the fact that $p_g \geq c_g$ in equilibrium, otherwise generics would have no incentives to enter.

$(3\beta + \gamma(2N-1))p_g - c_g > 4\gamma p_g - c_g > p_g - c_g > 0 \Leftrightarrow 4\gamma > 1 \Leftrightarrow \gamma > 0.25$ ■

To find the **equilibrium quantity levels**:

$$q_i = \left(\kappa \cdot \alpha_i - \tau \sum_{k \neq i} \alpha_k\right) - \kappa \cdot p_i + \tau \sum_{k \neq i} p_k$$

$$q_g = (\kappa \cdot \alpha_g - \tau \cdot \alpha_0 - \tau \cdot (N-1) \cdot \alpha_g) - \kappa \cdot p_g + \tau \cdot p_0 + \tau \cdot (N-1) \cdot p_g$$

$$q_g = \kappa \cdot \alpha_g - \tau \cdot \alpha_0 - \tau \cdot (N-1) \cdot \alpha_g + \tau \cdot p_0 - (\kappa - \tau \cdot (N-1)) \cdot p_g$$

$$q_g = \kappa \cdot \alpha_g - \tau \cdot \alpha_0 - \tau \cdot (N-1) \cdot \alpha_g + \tau \cdot p_0 - (\kappa - \tau \cdot (N-1)) \cdot p_g$$

$$\kappa \cdot \alpha_g - \tau \cdot \alpha_0 - \tau \cdot (N-1) \cdot \alpha_g + \tau \cdot p_0 = p_g(2\kappa - \tau \cdot (N-1)) - \kappa \cdot c_g$$

$$q_g = p_g(2\kappa - \tau \cdot (N-1)) - \kappa \cdot c_g - (\kappa - \tau \cdot (N-1)) \cdot p_g$$

$$q_g = p_g(2\kappa - \tau \cdot (N-1) - \kappa + \tau \cdot (N-1)) - \kappa \cdot c_g = \kappa \cdot (p_g - c_g) \quad [8]$$

Therefore:

$$\Pi_g = (p_g - c_g) q_g = \kappa \cdot (p_g - c_g)^2 - F$$

$$\frac{\partial \Pi_g}{\partial N} = \frac{\partial \Pi_g}{\partial p_g} \frac{\partial p_g}{\partial N} = 2\kappa \cdot (p_g - c_g) \frac{\partial p_g}{\partial N} < 0$$

Since $\frac{\partial p_g}{\partial N} < 0$ and price mark-up is positive $p_g - c_g > 0$, generic profits are decreasing in the number of entrants.

$$\Pi_g = \kappa \cdot (p_g - c_g)^2 - F$$

Plugging in $p_g^*(p_0) = \frac{\kappa \cdot c_g + \kappa \cdot \alpha_g - \tau(\alpha_0 + (N-1) \cdot \alpha_g) + \tau \cdot p_0}{2\kappa - \tau \cdot (N-1)}$

$$\Pi_g^* = \kappa \cdot \left\{ \frac{\kappa \cdot c_g + \kappa \cdot \alpha_g - \tau(\alpha_0 + (N-1) \cdot \alpha_g) + \tau \cdot p_0}{2\kappa - \tau \cdot (N-1)} - c_g \right\}^2 - F$$

Finding 3. Generic profits are decreasing in fixed costs of entry and the marginal cost of generic manufacturers.

$$\frac{\partial \Pi_g^*}{\partial c_g} = 2\kappa \cdot \left\{ \frac{\kappa \cdot c_g + \kappa \cdot \alpha_g - \tau(\alpha_0 + (N-1) \cdot \alpha_g) + \tau \cdot p_0}{2\kappa - \tau \cdot (N-1)} - c_g \right\} \left(\frac{\kappa}{2\kappa - \tau \cdot (N-1)} - 1 \right)$$

$$\frac{\partial \Pi_g^*}{\partial c_g} = 2\kappa \cdot (p_g - c_g) \left(\frac{\kappa}{2\kappa - \tau \cdot (N-1)} - 1 \right) < 0$$

Since $p_g > c_g$ and $\frac{\kappa}{2\kappa - \tau \cdot (N-1)} - 1 = \frac{\beta + \gamma(N-1)}{2\beta + \gamma(N-1)} - 1 < 0$. ■

Finding 4. Generic profits are increasing in α_g.

Proof:

$$\frac{\partial \Pi_g^*}{\partial \alpha_g} = 2\kappa \cdot \left\{ \frac{\kappa \cdot c_g + \kappa \cdot \alpha_g - \tau(\alpha_0 + (N-1) \cdot \alpha_g) + \tau \cdot p_0}{2\kappa - \tau \cdot (N-1)} - c_g \right\} \{\kappa - \tau \cdot (N-1)\}$$

$$\frac{\partial \Pi_g^*}{\partial \alpha_g} = 2\kappa \cdot \{p_g - c_g\} \beta > 0. \blacksquare$$

Π_g^* can be expressed in terms of the parameters β, γ by using

$$p_g(p_0) = \frac{(c_g + \alpha_g)(\beta + \gamma(N-1)) - \gamma \cdot \alpha_0 - \gamma \cdot (N-1)\alpha_g + \gamma \cdot p_0}{(\beta - \gamma)(\beta + \gamma N)(2\beta + \gamma(N-1))} \text{ and}$$

$$\kappa = \frac{\beta + \gamma \cdot N - \gamma}{(\beta - \gamma)(\beta + \gamma \cdot N)}$$

$$\Pi_g^* = \frac{\beta + \gamma \cdot N - \gamma}{(\beta - \gamma)(\beta + \gamma \cdot N)} \cdot \left(\frac{(c_g + \alpha_g)(\beta + \gamma(N-1)) - \gamma \cdot \alpha_0 - \gamma \cdot (N-1)\alpha_g + \gamma \cdot p_0}{(\beta - \gamma)(\beta + \gamma N)(2\beta + \gamma(N-1))} - c_g \right)^2 - F$$

Market entry decision of generic firms depends on the expected profit levels. If returns are sufficient to cover the fixed entry cost, i.e. if profits are positive, generics decide to enter[156].

Since $\frac{\partial \Pi_g}{\partial N} < 0$, generic profits will decrease as the number of generics increases. The maximum number of generics that the market can bear is given by $\Pi_g^*(N\max) = 0$. Nmax is given by the root of the polynomial:

$$\frac{\beta + \gamma \cdot N - \gamma}{(\beta - \gamma)(\beta + \gamma \cdot N)} \cdot \left(\frac{(c_g + \alpha_g)(\beta + \gamma(N-1)) - \gamma \cdot \alpha_0 - \gamma \cdot (N-1)\alpha_g + \gamma \cdot p_0}{(\beta - \gamma)(\beta + \gamma N)(2\beta + \gamma(N-1))} - c_g \right)^2 - F = 0$$

Price optimization for the branded product:

$\Pi_0 = (p_0 - c_0) q_0$, where $q_0 = \left(\kappa \cdot \alpha_0 - \tau \sum_{k \neq i} \alpha_k \right) - \kappa \cdot p_0 + \tau \sum_{k \neq i} p_k$

$$q_0 = (\kappa \cdot \alpha_0 - \tau N a_g) - \kappa \cdot p_0 + \tau N \cdot p_g(p_0)$$

Plugging in $p_g(p_0) = \frac{\kappa \cdot c_g + \kappa \cdot \alpha_g - \tau(\alpha_0 + (N-1) \cdot \alpha_g) + \tau \cdot p_0}{2\kappa - \tau \cdot (N-1)}$

[156] Fixed market entry costs represent research costs before drug launch (including bioequivalence tests).

$$q_0 = \left(\kappa \cdot \alpha_0 - \tau N a_g\right) - \kappa \cdot p_0 + \tau N \cdot \frac{\kappa \cdot c_g + \kappa \cdot \alpha_g - \tau\left(\alpha_0 + (N-1)\cdot \alpha_g\right) + \tau \cdot p_0}{2\kappa - \tau \cdot (N-1)}$$

$$q_0 = \kappa \cdot \alpha_0 - \tau N a_g + \tau N \cdot \frac{\kappa \cdot c_g + \kappa \cdot \alpha_g - \tau\left(\alpha_0 + (N-1)\cdot \alpha_g\right)}{2\kappa - \tau \cdot (N-1)} - \left(\kappa - \frac{\tau}{2\kappa - \tau \cdot (N-1)}\right) \cdot p_0$$

$$q_0 = \left(\kappa - \frac{\tau^2 N}{2\kappa - \tau \cdot (N-1)}\right) \cdot \alpha_0 - \tau N \left(\frac{\kappa + 2\tau}{2\kappa - \tau \cdot (N-1)}\right) a_g + \tau N \cdot \frac{\kappa \cdot c_g}{2\kappa - \tau \cdot (N-1)} - \left(\kappa - \frac{\tau}{2\kappa - \tau \cdot (N-1)}\right) \cdot p_0$$

$\Pi_0 =$

$$\left(p_0 - c_0\right)\left\{\left(\kappa - \frac{\tau^2 N}{2\kappa - \tau(N-1)}\right)\alpha_0 - \tau N \left(\frac{\kappa + 2\tau}{2\kappa - \tau(N-1)}\right) a_g + \tau N \frac{\kappa \cdot c_g}{2\kappa - \tau(N-1)} - \left(\kappa - \frac{\tau}{2\kappa - \tau(N-1)}\right) p_0\right\}$$

$$\frac{\partial \Pi_0}{\partial p_0} = \left(p_0 - c_0\right)\left(-\kappa + \frac{\tau}{2\kappa - \tau(N-1)}\right) +$$

$$\left(\kappa - \frac{\tau^2 N}{2\kappa - \tau(N-1)}\right)\alpha_0 - \tau N \left(\frac{\kappa + 2\tau}{2\kappa - \tau(N-1)}\right) a_g + \tau N \frac{\kappa \cdot c_g}{2\kappa - \tau(N-1)} - \left(\kappa - \frac{\tau}{2\kappa - \tau(N-1)}\right) p_0 = 0$$

$$\Rightarrow -2p_0\left(\kappa - \frac{\tau}{2\kappa - \tau(N-1)}\right) + c_0\left(\kappa - \frac{\tau}{2\kappa - \tau(N-1)}\right) + \left(\kappa - \frac{\tau^2 N}{2\kappa - \tau(N-1)}\right)\alpha_0 - \tau N \left(\frac{\kappa + 2\tau}{2\kappa - \tau(N-1)}\right) a_g + \tau N \frac{\kappa \cdot c_g}{2\kappa - \tau(N-1)} = 0$$

$$p_0 = \frac{2\kappa - \tau(N-1)}{2\left(2\kappa^2 - \kappa\tau(N-1) - \tau\right)}\left\{c_0\left(\kappa - \frac{\tau}{2\kappa - \tau(N-1)}\right) + \left(\kappa - \frac{\tau^2 N}{2\kappa - \tau(N-1)}\right)\alpha_0 - \tau N \left(\frac{\kappa + 2\tau}{2\kappa - \tau(N-1)}\right) a_g + \tau N \frac{\kappa \cdot c_g}{2\kappa - \tau(N-1)}\right\}$$

$$p_0 = \frac{2\kappa - \tau(N-1)}{2\left(2\kappa^2 - \kappa\tau(N-1) - \tau\right)}\left\{c_0\left(\kappa - \frac{\tau}{2\kappa - \tau(N-1)}\right) + \left(\kappa - \frac{\tau^2 N}{2\kappa - \tau(N-1)}\right)\alpha_0 - \tau N \left(\frac{\kappa + 2\tau}{2\kappa - \tau(N-1)}\right) a_g + \tau N \frac{\kappa \cdot c_g}{2\kappa - \tau(N-1)}\right\}$$

$$p_0 = \frac{c_0\left(2\kappa^2 - \kappa\tau(N-1) - \tau\right) + \left(2\kappa^2 - \kappa\tau(N-1) - \tau^2 N\right)\alpha_0 - \tau N(\kappa + 2\tau)a_g + \tau N\kappa c_g}{2\left(2\kappa^2 - \kappa\tau(N-1) - \tau\right)}$$

Plugging this back into the reaction function of generics:

$$p_g(p_0) = \frac{\kappa \cdot c_g + \kappa \cdot \alpha_g - \tau\left(\alpha_0 + (N-1)\cdot\alpha_g\right) + \tau \cdot p_0}{2\kappa - \tau\cdot(N-1)}$$

$$p_g(p_0) = \frac{\kappa \cdot c_g + \kappa \cdot \alpha_g - \tau\left(\alpha_0 + (N-1)\cdot\alpha_g\right)}{2\kappa - \tau\cdot(N-1)} + \tau \cdot \left\{\frac{c_0\left(2\kappa^2 - \kappa\tau(N-1) - \tau\right) + \left(2\kappa^2 - \kappa\tau(N-1) - \tau^2 N\right)\alpha_0 - \tau N(\kappa + 2\tau)a_g + \tau N\kappa c_g}{2\left(2\kappa^2 - \kappa\tau(N-1) - \tau\right)}\right\}.$$

$$p_g = \left\{\kappa + \tau \cdot \frac{\tau N\kappa}{2\left(2\kappa^2 - \kappa\tau(N-1) - \tau\right)}\right\}\cdot c_g + \tau \cdot \frac{2\kappa^2 - \kappa\tau(N-1) - \tau}{2\left(2\kappa^2 - \kappa\tau(N-1) - \tau\right)}c_0 + \left(\frac{\kappa - \tau(N-1)}{2\kappa - \tau\cdot(N-1)} - \tau\cdot\frac{\tau N(\kappa + 2\tau)}{2\left(2\kappa^2 - \kappa\tau(N-1) - \tau\right)}\right)\alpha_g - \left(\tau - \tau\frac{2\kappa^2 - \kappa\tau(N-1) - \tau^2 N}{2\left(2\kappa^2 - \kappa\tau(N-1) - \tau\right)}\right)\alpha_0.$$

$$p_g = \left\{1 + \frac{\tau^2 N}{2\left(2\kappa^2 - \kappa\tau(N-1) - \tau\right)}\right\}\kappa c_g + \frac{\tau}{2}c_0 + \left(\frac{\kappa - \tau(N-1)}{2\kappa - \tau\cdot(N-1)} - \frac{\tau^2 N(\kappa + 2\tau)}{2\left(2\kappa^2 - \kappa\tau(N-1) - \tau\right)}\right)\alpha_g - \left(1 - \frac{2\kappa^2 - \kappa\tau(N-1) - \tau^2 N}{2\left(2\kappa^2 - \kappa\tau(N-1) - \tau\right)}\right)\tau\alpha_0. +$$

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