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Essays on Pharmaceutical Economics

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Essays on Pharmaceutical Economics

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Abstract

This thesis presents an introduction, Chapter One, and three research papers on pharmaceutical economics.

In Chapter Two I examine the effect of the regulations restricting price increases on the evolution of pharmaceutical prices. A novel theoretical model shows that this policy leads firms to price new drugs with uncertain demand above the expected value initially. Price decreases after drug launch are more likely, the higher the uncertainty. I empirically test the model's predictions using data from the Canadian pharmaceutical market. The level of uncertainty is shown to play a crucial role in drug pricing strategies.

In Chapter Three, I analyze the timing of approvals and submissions of new pharmaceutical products in Canada and explore possible reasons for delays based on available data. Some commentators have claimed that Health Canada's process for approving new drugs is excessively slow, thereby delaying access to these drugs by Canadians. However, I found that submission of new drugs to Health Canada for approval is systematically delayed compared with submissions to regulatory agencies in the United States and the European Union, which delays the availability of new drugs in Canada. I also explore the likely effects of a harmonized process of submissions between the US Food and Drug Administration and Health Canada.

In Chapter Four, I investigate the effect of value-based pricing (VBP) schemes on the behaviour of innovative pharmaceutical companies when their new technology offers potential to be used for more than one patient type. I allow for the division of patients to be determined both exogenously and endogenously. When the division of patients is determined exogenously, the payer needs to consider two effects in choosing the pricing schemes: distortion in seeking approval and distortion in the prices of incumbent technologies. Marginal value-based pricing, in

which price is set based on the health benefits of the patient-type with the smallest health benefits, brings both distortions. Average value-based pricing, where the price is set based on the average health benefits across patient types, does not deprive any patient type from the new technology, though it brings price distortion for both patient types. Differential value-based pricing, in which price of the new technology for each patient type is set separately, does not create any distortion. When the division of patient populations is determined endogenously, the pricing schemes do not affect the behaviour of manufacturers in seeking approval and validating marker. However, value-based pricing by itself and the cost of validating marker are the main determinants of the manufacturer's behaviour.

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Chapter One: Introduction

1.1 Introduction

Pharmaceutical markets are bedevilled by various market failures, resulting in extensive regulation in all developed countries. Innovative pharmaceutical companies face a heavily regulated environment in all aspects of their activities from the start of research and development to the last phase of selling the product to the final consumers, i.e. patients. When bringing a new pharmaceutical product to the market, innovative firms have to comply with safety, efficacy, and manufacturing requirements of regulatory agencies in each jurisdiction. After receiving marketing approval, promotion of new products is also regulated to mitigate the asymmetry of information between firms on one side and patients and physicians on the other. Pricing of pharmaceuticals is also regulated in one way or another in many countries. Although patent systems are in place to help manufacturers to recoup their large initial R&D costs, insurance coverage make patients insensitive to price, which ultimately results in insurers applying limits to their coverage. Although all major aspects of pharmaceutical companies are regulated, this regulation may have unexpected outcomes. A key policy issue is how to design regulation to balance the affordability and innovation into new pharmaceutical products.

The main goal of this thesis is to assess the effect of regulation in pharmaceutical markets on different aspects of firms' decisions. The second and fourth chapters of the thesis address the behaviour of companies when faced with common price regulations implemented in many countries. The third chapter deals with the timing of market access as pharmaceuticals products reach some markets later than others.

A common price regulation implemented in many countries is a form of price-cap regulation. This system starts with constraining initial prices and subsequently putting a limit, such as the rate of inflation, on price increases afterwards. Many countries, including Canada, Sweden, and Spain use such a scheme to contain the cost of acquiring new pharmaceuticals. Even in the United States, which has relatively little use of price regulations, the Omnibus Budget Reconciliation Act of 1990 limits price increases of brand drugs sold to Medicaid to the rate of inflation. Despite its widespread use, little is known about the effect of price-cap regulation on the price evolution of new pharmaceuticals.

In the second chapter, I provide a simple theoretical model to investigate the reaction of pharmaceutical companies to price-cap regulation. The main focus of this chapter is the uncertainty of demand in this environment. The theoretical model shows that the price cap policy leads to high introductory prices for drugs with uncertain demand as firms know they will be unable to increase prices later. Consistent with theory, the level of uncertainty associated with a drug is found to be a crucial determinant of price evolution in the Canadian pharmaceutical market. Given that the established price in the introductory year is the highest achievable price in the drug's life cycle in a regulated market with price-cap regulation, drugs facing uncertainty in their market reception tend to start with a high introductory price. Pharmaceutical firms will adjust their prices if the market reception is unfavourable. This "price exploration strategy" is followed only in the case of young innovative drugs because the old ones are exposed to less uncertainty.

Value-based pricing (VBP) schemes, in which the price of a health technology is linked explicitly to its health benefits, has been extensively and explicitly used in pricing new pharmaceuticals in many countries, and is also on the verge of being used in other segments of

health care market in the US. The main idea of such pricing scheme is to liberate price from unobservable and sometimes proprietary information of companies, such as research and development (R&D) cost and production cost, and focus on the health benefits that each health technology provides to patients. VBP is perceived to provide the right incentives to innovative companies to invest in the most valuable health technologies.

In the fourth chapter, I investigate the effect of VBP on the behaviour of a pharmaceutical company bringing a new drug beneficial to multiple patient types. I allow for the division of patient populations to be determined exogenously, in which case the drug is a "multi-indication technology", or endogenously, in which case it is a "multi-subgroup technology". The manufacturer decides which indications or subgroups to target and also how much information to generate, taking into account pricing schemes and the information requirement of the regulatory agencies and payers during the development process. The payer needs to consider two effects in choosing the pricing schemes in multi-indication technologies: distortion in seeking approval and distortion in the prices of incumbent and future technologies. For multi-subgroup technologies this chapter shows that the pricing schemes do not affect the behaviour of manufacturers in seeking approval and distinguishing subgroups. However, value-based pricing by itself and the cost of distinguishing patients from each other are the main determinants of the manufacturer's behaviour.

The lag in access of a country to new drugs may contribute to health outcomes of patients and health spending in that country. Price and safety regulations are often blamed for delay. However, launch delay consists of several components, including some under the control of pharmaceutical companies and others out of their control.

In the third chapter, I show that differences across jurisdictions in approval-processing times played a small role in the launch times across countries. Instead, differences in the timing of drug submissions were an important factor. Although the mean time to approval was about 90 days longer in Canada than in other two big markets, the US and the EU, the mean submission delay in Canada was much longer than in the other two jurisdictions. For drugs that were ultimately approved in Canada and in at least one of the other jurisdictions, the mean delay from first submission in either foreign jurisdiction to submission in Canada was 540 days, compared with 106 days for the US and 215 days for the EU. I also examine several different possible reasons for delays in submission of new drug files. I find that corporate capacity and the priority status of new drugs appear to be important determinants of submission delay.

Chapter Two: Price-Cap Regulation, Uncertainty and the Price Evolution of New Pharmaceuticals

With Aidan Hollis[1]

2.1 Introduction

A common regulatory intervention in pharmaceutical markets is to prohibit price increases above the rate of inflation. Following Abbott (1995), we label this policy "price-cap regulation". This chapter offers a simple theoretical model of price-cap regulation in a context with a new drug facing uncertain demand and an empirical test of the model using Canadian data. The theoretical model shows that the policy leads to high introductory prices for drugs with uncertain demand because of the inability to increase prices. Surprisingly, we show that welfare effects can be positive, to the extent that price influences consumption, and price-cap regulation can thus be efficiency enhancing because it shifts consumption toward higher quality drugs. Consistent with theory, our empirical analysis of Canadian drug prices shows that price-cap regulation selectively affects drugs with uncertain demand: Drugs with new active substances have a bimodal distribution of price evolution, either staying at the initial high price or else dropping their price substantially after the drug is introduced to the market. In comparison, new drugs with known demand—such as Reformulations of Old drugs—have a unimodal distribution of price evolution, with no substantial decreases.

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[1] A short version of this chapter is published in Health Economics:
Shajarizadeh, A., & Hollis, A. (2015). Price-cap Regulation, Uncertainty and the Price Evolution of New Pharmaceuticals. *Health economics*, *24*(8), 966-977.

Most industrialized countries regulate pharmaceutical prices in one way or another. The most common regulation starts with constraining initial prices. Price increases after launch are then restricted according to price-cap regulation, typically allowing for increases at the rate of inflation (Jacobzone, 2000). Even in the USA, which has relatively little use of price regulations, the Omnibus Budget Reconciliation Act of 1990 limits price increases of brand drugs sold to Medicaid to the rate of inflation. Pharmaceutical expenditures have been one of the fastest-growing components of health care expenditures globally, suggesting that understanding price-cap regulation in pharmaceutical markets is important. Despite its widespread use, little is known about the effect of price-cap regulation on the price evolution of new pharmaceuticals.

Although safety and efficacy of all new drugs are assessed by regulatory agencies before coming to the market, these assessments do not eliminate all uncertainty. The limited size and short duration of premarketing clinical trials mean that not everything can be fully learned about the safety profile (side effects and drug–drug interactions) of a new drug before its approval. Patients are carefully screened and closely monitored throughout premarketing clinical trials, which reduces the risk of poor product choice and poor compliance in this controlled environment, relative to situations in real world (U.S. Food and Drug Administration, 2007).[2] Much more information, including a more complete safety profile of drugs, is learned through wide usage by patients after approval.

Assuming the safety standard is met, firms are required to verify only that the new drug is more effective than placebo, not more effective than existing products. Thus, there is a great deal

[2] Clinical trials are conducted on a relatively small group of selected patients. Therefore, little information is revealed about safety and efficacy of drugs on understudied populations such as patients who have multiple health problems or chronic illnesses.

of uncertainty for patients, physicians, payers, and even firms regarding the likely population and their use of drugs, or in short, the factors that influence demand for the drug after approval. As patients with heterogeneous characteristics use a newly approved drug, information is acquired about the match between a new drug, its indications, and patients with different characteristics.

The extent of demand uncertainty, however, varies across drugs and across time. First, more novel drugs face higher uncertainty, as consumers have less experience with the use of similar products and firms have less information about demand parameters. Second, the less the cumulative use of a specific drug and the shorter the time since first usage, the less knowledge there is about the drug itself and its effects. Empirically, safety warnings are more likely to be issued within the early years following a drug's introduction (Lasser *et al*., 2002). We identify the effect of this uncertainty on the price evolution of drugs using novelty and the experience of drugs in the US market.

This chapter is the first study on the price evolution of patented pharmaceuticals in Canada. Drug companies encounter two distinct hurdles in freely implementing their pricing strategies in the Canadian market: The Patented Medicine Prices Review Board (PMPRB) and provincial drug plans. The PMPRB reviews the introductory prices set by firms and does not allow any increase in real prices following introduction. Public drug plans also limit price increases. Therefore, restrictions on initial prices and on price increases in the following years, as well as cost-sharing policies, may affect the pricing strategies of drug companies. We find that uncertainty associated with new drugs is an important factor in determining the pricing strategies of drugs in Canada. Innovative drugs are marketed in Canada with high introductory prices because firms know that price increases in the following years will not be permitted. Price-cap

regulation motivates pharmaceutical firms to "explore" the highest achievable price in the market, by setting a high price in the introductory year and adjusting it down only if needed.

These findings are in contrast with the result of previous studies in the less heavily regulated market of the USA. Not surprisingly, the strategies of drug companies depend on the structure and regulatory context of the pharmaceutical market in each jurisdiction and vary between Canada and the USA.

This chapter is organized as follows. In the next section, we review the literature on the pricing strategies of new pharmaceutical products. Section 3 describes the data used in this chapter as well as the empirical model to be estimated. In section 4, we discuss the empirical results of the model. Section 5 concludes the chapter.

2.2 Literature on the dynamics of drug prices

The literature on the dynamics of pharmaceutical pricing reflects the different regulatory environments across countries. Reekie (1978), considering new drugs introduced to the US drug market between 1958 and 1975, shows that firms set their pricing strategies based on therapeutic novelty. Using univariate analysis, he finds that major breakthrough drugs come to the market with high prices (relative to their rivals) with a gradual reduction over the product life cycle. This pricing strategy is called "skimming" because it seeks to obtain high prices from consumers with a high willingness to pay.[3] Conversely, imitative drugs were found to follow a "penetration

[3] We doubt that the "skimming" strategy has much relevance for drug pricing in the modern era. Skimming may make sense in durable goods markets, in that the monopolist offers the product initially at a high price, trying to attract consumers with a high willingness to pay. The monopolist then drops the price over time to attract consumers with lower willingness to pay. Coase (1972) famously conjectured that this strategy was flawed, since consumers with a high willingness to pay would simply wait for the price reduction. Even ignoring Coase's objection, most drugs do not resemble durable goods. The only class of pharmaceutical products that are "durable" is vaccines. Price discrimination across periods does not make sense if there is a new crop of consumers each period with the same distribution of willingness to pay. It is more likely that in the time period analyzed by Reekie (1978), when there was no cost effectiveness analysis by insurers, high initial prices were used to signal quality.

pricing" strategy; prices of drugs with minor advances relative to their rivals are set at a low level on market launch. The prices of these imitator drugs then increase over time. The intuitions for these two different pricing strategies are based on the seminal marketing analysis by Dean (1969).

Weston (1979) emphasizes another competitive aspect of the pricing behaviour of firms by showing that the decrease in prices of innovative drugs is responsive to the entry of new drugs in the same therapeutic class. Lu and Comanor (1998) examine the pricing strategies of firms in a multivariate analysis. Considering new drugs introduced to the US market between 1978 and 1987, Lu and Comanor find that therapeutic novelty, the number of substitutes in a therapeutic class, and the anticipated number of repeat purchases are the main determinants of pricing strategies for new patented drugs. As a result, unregulated pharmaceutical markets can be characterized as oligopolistic markets where firms have some market power in pricing their products. Market power rises with the level of product novelty and falls as more branded competitors enter the market. Switching costs play a role for chronic drugs with repeat purchases.

Frank and Salkever (1997) show that branded drugs facing generic competitors increase their price to take advantage of the inelastic segment of the market, while competition reduces the price of generic drugs. As a result, off-patent branded competitors with generic rivals and patented branded drugs could have different effects on the pricing strategies of a new drug entering the same therapeutic class. Lu and Comanor (1998) find that while competition from patented branded drugs depresses the prices of new drugs, competition from off-patent drugs with generic rivals increases prices.

While the previous studies examine pricing strategies in the relatively less regulated US market, their predictions might not carry through in markets with more intrusive price regulations. Abbott (1995) studies the effect of implementing a policy restricting price increases in the pharmaceutical industry. Abbott compares the optimal prices of an unregulated firm to the optimal prices of a firm facing price-cap regulation over the life of the product. In doing so, he estimates a demand function for this industry based on a sample of 35 drugs during the 1970s and 1980s for which the average price increased substantially over time. He interprets the price increase as being caused by an unexplained decrease in price elasticity and assumes that this is a universal property of drugs. He argues that prohibiting price increases through price-cap regulation will cause firms to set a high price initially. Borrell (2003) extends this analysis within a monopolistically competitive setting with formularies and finds a similar result. In this chapter, we do not make any assumptions about changes in elasticity but incorporate the uncertainty that firms face when introducing a new drug to the market. Moreover, we allow this uncertainty to vary across drugs.

Ridley (2011) analyzes regulation of price increases in a more general context, incorporating forward looking consumers and switching costs, which are relevant for many medications used for chronic conditions. He shows that price regulation can help both consumers and the firm because the regulations allow the firm to commit to a lower price path and attract more consumers at launch, extending the seminal results of Farrell and Gallini (1988).

Empirical papers assessing the initial prices of firms in price-cap regulated markets find that therapeutic novelty is not an important determinant of initial prices in this market framework. Lexchin (2006) observes that “Me-too” drugs introduced in the Canadian market between 1994 and 2003 are priced close to their brand-name substitutes in the same therapeutic

class. Moreover, the prices of new drugs are lower only when there are more than four competitors in the class. Lopez-Valcarcel and Puig-Junoy (2012) studied the regulated Spanish market, in which, as they noted, the rarely adjusted price cap is a key regulatory constraint. They find that therapeutic novelty does not seem to impact price significantly.

Ekelund and Persson (2003) examine the pricing strategies of new drugs introduced into Sweden between 1987 and 1997. Sweden, like Canada and Spain, had a system of price-cap regulation. They find that the average relative introductory prices were higher for new drugs in Sweden than the USA, while real prices declined over time for both innovative and Me-too drugs, with a greater rate for innovative ones. Their results show that market structure factors, such as the number of branded competitor with and without generic rivals, are not statistically significant determinants of initial prices and the price evolution of new drugs. Their results on Swedish price changes are consistent with our findings in the Canadian market, which gives us some confidence that the empirical findings in this chapter are robust. This chapter expands their results to compare across different degrees of uncertainty and offers a simple novel theoretical model to explain the results.

2.3 The pharmaceutical market in Canada

As a precondition for market access, a manufacturer must submit substantive scientific evidence of a new drug's safety, efficacy and quality to Health Canada.[4] Health Canada categorizes new drugs as either New Active Substance (NAS) or other. Drugs in the NAS category contain a therapeutic substance that has never before been approved for marketing in Canada. Moreover, Health Canada expedites its review process (under Priority status) for drugs with no substitutes

[4] Therapeutic Products Directorate is the section responsible for regulation on pharmaceuticals and medical devices meant for human use.

in the market or with a significant increase in efficacy and/or significant decrease in risk relative to existing drugs.

Following this step, the PMPRB reviews prices set by the manufacturer to ensure that they are not "excessive". This agency reviews prices per unit for each drug at the Drug Identification Number (DIN) level.[5] The price-regulatory role of the PMPRB is twofold. First, it assesses whether the prices of newly patented drugs are compliant with its guidelines. Roughly speaking, if a similar drug is already marketed in Canada, then the price of the existing drug becomes the benchmark for the new drug and the introductory price is not permitted to exceed this benchmark. Otherwise, the price of the same drug in other countries will be taken as a benchmark. Second, the PMPRB requires that price increases of patented medicines not exceed the increase in the Consumer Price Index.[6]

Most Canadians have drug insurance through public or private plans. Each province runs its own drug plan to provide coverage to seniors and families on social assistance. The federal government also provides drug benefits to special groups such as First Nations persons and veterans. Similarly, many employers offer drug benefits to employees and their dependents. It is estimated that between 96% and 98% of Canadians have access to drug insurance in one form or another (Frasr Group Tristat Resources, 2002; Kapur & Basu, 2005). However, drug plans are different in the level of coverage and policies regarding expenditure controls.

All public and some private plans have in place a formulary, a list of approved drugs for which an insurer will pay. Governments decide whether to include a drug on the public

[5] DIN identifies drug products by their trade name, dosage form, strength, manufacturer, and is assigned by Health Canada.
[6] For more detailed information about the PMPRB price review process, see PMPRB (2012).

formulary, and on the status of listing (i.e. with or without restrictions) after reviewing the relevant economic and clinical information. The clinical and cost-effectiveness evidence of new drugs are also rigorously reviewed by the Common Review Drug, a publicly funded process, and a listing recommendation is made to all provincial formularies except Quebec, which operates its own similar but independent scheme. Most private plans include almost all drugs approved by Health Canada in their formularies (Rovere & Skinner, 2012).

Price increases for drugs listed in the public formulary are also limited by the provincial insurers. For example, the Ontario government permits price increases for listed drugs only if justified by substantial increases in raw material costs, all supported by extensive analytical reports and manufacturing details.[7]

Recently, some provincial plans have instituted new mechanisms in dealing with brand companies, requiring them to provide confidential rebates in exchange for their drugs being listed in the formulary. In 2006, the province of Ontario started direct negotiation with pharmaceutical firms on rebates for patented medicines (Silversides, 2009). These rebates are to be paid by firms to the drug plan for each unit of drugs reimbursed. Facing the "best available price" clause implemented by province of Quebec and the potential reaction of other provinces, pharmaceutical firms and the province of Ontario have kept the rebates confidential.[8] As a result, the prices reimbursed to pharmacies no longer reflect the prices that pharmaceutical firms

[7] Ontario Ministry of Health and Long-Term Care, "Price Increase Criteria and Request Process" 20 November 2008, last accessed February 7 2013 at http://www.health.gov.on.ca/english/providers/program/drugs/drug_submissions/price_increase_requests/process_price_increase_requests.pdf

[8] According to this clause that is in Quebec's legislation, prices for Quebec's drug plan cannot be higher than the price paid by other drug plans. After revelation of confidential rebates from 47 drug companies to Ontario in 2010, the Quebec government threatened legal action against any company that had not given the lowest price to Quebec (The Globe and Mail, April 09, 2010).

receive. Fortunately, in the data used in the chapter, confidential rebates were not a substantial concern: only Ontario was receiving them, only for some drugs, and that only in later years.

Pharmaceutical markets are unusual in that one party (the patient) consumes, a second party (the physician) determines what is to be consumed, and a third party (the insurer) pays. Canadian insurance plans engage in very limited cost-sharing (Grootendorst, 2002). This complex system reduces price elasticity, so that profit-maximizing prices may be extremely high. The insensitivity to prices justifies price regulation and the limitation of what is listed in the provincial formularies, since otherwise firms would have incentives to increase prices almost without limit.

2.4 A Simple Theoretical Model

In this section, we develop a simple theoretical model in which a firm bringing a new drug to the market faces considerable uncertainty about the demand.[9] The firm learns the market reception to the new drug over time and reconciles its pricing strategy with the new evidence about demand. The first part of this section focuses only on demand uncertainty, abstracting from market structure factors. Starting analysis with an unregulated market, we show how firms' pricing strategy changes in a price-cap regulated market when the demand is uncertain. We then incorporate market structure factors to the model.

In the following model, we assume that there are two periods. In the first period, consumers, who are uncertain about safety and effectiveness of new drugs, start using the new drug. Firms set a price based on the expected reception of the market to their product, i.e. expected demand. In the second period, the demand function for the new drug is fully known by

[9] Note that this assumption differs from that of Ridley (2011) since we do not assume any switching costs: consumer demand is independent across periods.

firms. In this chapter, we do not consider the learning process or dynamics through which the uncertainty is resolved, but focus on the pricing strategy of firms facing this uncertainty and implication of that for pricing strategies of firms in markets with price-cap regulation.[10]

2.4.1 Demand function with uncertainty

We treat physicians, patients and insurers as a decision-making unit, abstracting from the principle-agent problems between insurers, physicians and patients. These "composite consumers" care about safety and effectiveness profile of a drug and its price and are to some extent willing to trade off over the two. The safety and effectiveness profile of a drug is simply called "quality" in this section. If the quality is too low, the insurer may impose restrictions or not list the drug on the formulary at all unless the price is reduced. In this model, consumers are uncertain about the true quality of the new drug, but start with a set of beliefs. More specifically, they know the possible qualities that the drug can take. Therefore, consumers start using the new drug in the launch period based on their initial beliefs. For tractability, we assume that consumers are risk-neutral and the drug can take only two different qualities: high quality q_h with the probability λ or low quality q_l with probability $1-\lambda$.[11] For any given λ, quality uncertainty can be measured by $q_h - q_l$. In the first period, expected quality is assumed to be the probability weighted mean of q_h and q_l.

Since consumers care about both price and quality, the demand function for a drug has the following form:

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[10] There is a growing literature on the learning process through which the initial uncertainty of a new drug is resolved. For a literature review, see Manchanda *et al.* (2005).

[11] We make no particular assumptions about probabilities, but use this simple distribution to generate uncertainty about the quality of the drug.

$$x_1 = \alpha - \beta p_1 + \gamma E(q)$$
$$x_{2i} = \alpha - \beta p_{2i} + \gamma q_i \, , i = h, l \tag{2.1}$$

where x_t denotes the quantity demanded in period t, p_t the price in period t, and of course β and γ are positive. Subscript i denotes the realized quality of the drug in the second period. The quality measure in the first period is simply expected quality $E(q)$, while quality in the second period is the realization of quality for the drug q_h or q_l.

2.4.2 The firm's problem in an unregulated market

Firms maximize their profits in each period based on the available information about quality. Firms choose a single price based on expected quality in the first period. Seeing the realized quality in the second period and being able to increase prices, firms adjust the price according to the realized quality:

$$p_1^U = \frac{\alpha + \gamma E(q)}{2\beta}$$
$$p_{2i}^U = \frac{\alpha + \gamma q_i}{2\beta} \, , i = l, h \tag{2.2}$$

where the price changes are:

$$p_{2h}^U - p_1^U = \frac{\gamma(1-\lambda)}{2\beta}(q_h - q_l)$$
$$p_{2l}^U - p_1^U = -\frac{\gamma\lambda}{2\beta}(q_h - q_l) \tag{2.3}$$

Given this unregulated setting, prices rise or fall as uncertainty is resolved, with the average price remaining unchanged.

2.4.3 The firm's problem in a regulated market with upward price-rigidity

We now incorporate upward price-rigidity resulting from price-cap regulation into the model to assess its effect on the pricing strategies of the firms in each period. Upward price-rigidity limits the second period price to not exceed the first period price, i.e. $p_{2i} \leq p_1$. This constraint relates the price chosen in the first period to that in the second period, obliging firms to maximize the present discounted value of expected profit. We can write the optimization problem facing firms in a regulated market as:

$$\begin{aligned} \max_{p_1, p_{2h}, p_{2l}} \pi^R = & \left[\left(\alpha - \beta p_1 + \gamma E(q)\right) p_1\right] \\ & + \delta[(1-\lambda)(\alpha - \beta p_{2l} + \gamma q_l) p_{2l} + \lambda(\alpha - \beta p_{2h} + \gamma q_h) p_{2h}] \\ & s.t. \;\; p_{2i} \leq p_1 \end{aligned} \tag{2.4}$$

The second expression in the brackets is the second-period profits given either a low- or high-quality realization. $\delta > 0$ is the weight on the second period. (In principle, the second period could be much longer than the first period and δ could therefore be above 1.) The trade-off for firms is that, in order to reduce the cost of the constraint in the second period, they set a price in the first period on all new drugs that is higher (and less profitable) than the unregulated first period price.

The solution for the prices in the first and second period is:

$$\begin{aligned} p_1^R = p_{2h}^R &= \frac{\alpha + \gamma E(q)}{2\beta} + \frac{\gamma\delta\lambda(1-\lambda)}{2\beta(1+\delta\lambda)}(q_h - q_l) \\ p_{2l}^R &= \frac{\alpha + \gamma q_l}{2\beta} \end{aligned} \tag{2.5}$$

Notice that the first component of p_1^R is p_1^U and the second term is greater than zero. This means the first-period price given upward price-rigidity is higher than that given pricing

freedom. In other words, quality uncertainty combined with upward price-rigidity creates an incentive for firms to set a launch price higher than would be profit-maximizing in the absence of the upward price-rigidity. In the second period, after quality is revealed, p_{2h}^R does not change, and is below p_{2h}^U. On the other hand, the second period price of a low-quality drug is the same for regulated and unregulated markets.

Price changes from first period to the second period are:

$$\begin{aligned} p_{2h}^R - p_1^R &= 0 \\ p_{2l}^R - p_1^R &= -\frac{\gamma\lambda(1+\delta)}{2\beta(1+\delta\lambda)}(q_h - q_l) \end{aligned} \tag{2.6}$$

Uncertainty substantially influences the price dynamics of new drugs in a market with upward price-rigidity. If the quality of all drugs is known, or in effect, if the firm is certain about demand ($q_h = q_l = q$), then upward price-rigidity does not bind. As Abbott (1995) shows, in the case of certainty, the firm simply starts with the profit-maximizing price and keeps it over the life of the drug. This is a trivial result of upward price-rigidity. What is not quite so trivial is that the effect on the average price arises from uncertain quality in this model: the *average* price will fall in a market with upward price-rigidity, and the greater the uncertainty component $(q_h - q_l)$, the higher the launch price and the greater the average price reduction.

2.4.4 Welfare Implications

Generally, price control regulations are thought to damage welfare, but in this case upward price-rigidity may increase welfare.[12] The firm, in choosing a single price for both the first period and the second period if the quality is revealed to be high, must balance the change in profit in these

[12] This model does not consider the dynamic view about the incentives of innovative manufacturers for bringing a new drug to the market. However, price cap regulation does decrease expected profits, and would therefore reduce incentives for innovation.

two periods on the margin. Balancing these two effects leaves some positive surplus for consumers.

Expected welfare in the unregulated setting can be described as:

$$W^U = \frac{3}{2\beta}\left[\left(\frac{\alpha + \gamma E(q)}{2}\right)^2 + \delta\lambda\left(\frac{\alpha + \gamma q_h}{2}\right)^2 + \delta(1-\lambda)\left(\frac{\alpha + \gamma q_l}{2}\right)^2\right] \tag{2.7}$$

where the second and third terms represent the weighted welfare in the second period given either a high- or a low-quality realization. In the regulated setting, welfare is given by:

$$W^R = \frac{3}{2\beta}\left[\left(\frac{\alpha + \gamma E(q)}{2}\right)^2 + \delta\lambda\left(\frac{\alpha + \gamma q_h}{2}\right)^2 + \delta(1-\lambda)\left(\frac{\alpha + \gamma q_l}{2}\right)^2\right] + \left(\frac{\delta\lambda(1+\delta\lambda)}{2\beta}\right)\left(\frac{\gamma(1-\lambda)(q_h - q_l)}{2(1+\delta\lambda)}\right)^2 \tag{2.8}$$

The difference between W^R and W^U is given by:

$$W^R - W^U = \left(\frac{\delta\lambda(1+\delta\lambda)}{2\beta}\right)\left(\frac{\gamma(1-\lambda)(q_h - q_l)}{2(1+\delta\lambda)}\right)^2 > 0 \tag{2.9}$$

The reason for the increase in welfare under price-cap regulation is that the second-period price given the realization of high quality is lower in the regulated market than that in the unregulated market while the price in the first period is higher. Thus, the regulated market experiences greater utilization of the high-quality drug balanced against a smaller use of the drug with unknown quality in the first period. This creates a welfare gain because there is a greater benefit from increased use of the high-quality product than harm from reduced use of the product with lower expected quality. Given that the model's welfare function includes both profits and consumer surplus, it is important to appreciate that the welfare increase is not arising just because of lower price, but because the volume consumed of the high-quality product increases.

2.4.5 Price-cap regulation and market structure factors

In this section, we add market structure factors to the model. Suppose N represents competitive factors such as the number of branded substitutes in the market. The demand function in this situation becomes:

$$x_1 = \alpha - \beta p_1 + \gamma E(q) - \eta N_1$$
$$x_{2i} = \alpha - \beta p_{2i} + \gamma q_i - \eta N_2 \,, i = h, l \tag{2.10}$$

The profit-maximizing price in a price-cap regulated market is:

$$p_1^R = p_{2h}^R = \frac{\alpha + \gamma E(q) - \eta N_1}{2\beta} + \frac{\gamma\delta\lambda(1-\lambda)}{2\beta(1+\delta\lambda)}(q_h - q_l)$$
$$- \frac{\eta\delta\lambda}{2\beta(1+\delta\lambda)}(N_2 - N_1) \tag{2.11}$$
$$p_{2l}^R = \frac{\alpha + \gamma q_l - \eta N_2}{2\beta}$$

In this situation, the first-period price and second-period price given a high-quality realization are equal, or the price-cap restriction is binding, only when $\gamma(1-\lambda)(q_h - q_l) - \eta(N_2 - N_1) > 0$; the positive effect of quality uncertainty weighed by $(1-\lambda)$ outweighs the negative effect of market structure factors (the changes in N). Otherwise price dynamics would be determined only by market structure factors, as in an unregulated market. In this case, we would not see any effect of uncertainty.

Note that this is an extreme case in which N would have large negative effects on the price of a new drug. As Lu and Comanor (1998) show not all market structure factors have negative effect on prices. Moreover, Ekelund and Persson (2003) show that increased

competition did not reduce prices of new drugs in Sweden, a price-cap regulated market. When uncertainty is stronger than market structure factors, the price changes would be:

$$p_{2h}^R - p_1^R = 0$$
$$p_{2l}^R - p_1^R = -\frac{\gamma\lambda(1+\delta)}{2\beta(1+\delta\lambda)}(q_h - q_l) - \frac{\eta}{2\beta(1+\delta\lambda)}(N_2 - N_1) \quad (2.12)$$

Although the price change is similar for drugs with different uncertainties, the level of uncertainty $(q_h - q_l)$ determines the magnitude of decrease if the drug happens to be low-quality. For instance, for drugs with no uncertainty (i.e. $q_h - q_l = 0$) , the price path is determined by market structure factors, as in unregulated markets. Therefore, the expected price reduction for these drugs would be lower than for drugs with substantial uncertainty ($q_h - q_l \gg 0$).

In summary, this simple model generates several interesting predictions. First, the initial prices for drugs in a market with price-cap regulation will be, on average, higher than in markets without upward price rigidity when demand is uncertain. Second, prices in regulated markets should fall, on average, for products with unknown demand (and an ex ante unknown full-information price). The greater the uncertainty, the greater the expected price reduction is. The data that we have in this chapter allow us to explore only the second prediction. The first prediction is difficult to test because price comparisons across countries tend to be confounded by many other explanatory differences, including regulation of introductory prices and differential demand across countries.

2.5 Empirical Analysis

We describe in the succeeding subsections the identification strategy and then the data that are used in this chapter in the following subsections. The identification strategy relies on the

association between the demand uncertainty of a drug and its US experience and therapeutic novelty when listed by public drug plans in Canada.

2.5.1 Identification strategy

As our theoretical model shows, price-cap regulation influences price changes, mediated by the level of demand uncertainty:

$$\Delta P_j = \varphi + \delta(q_h - q_l)_j + \Delta X_j \beta + \varepsilon_j \tag{2.13}$$

where ΔP_j is the price change for drug j, $(q_h - q_l)_j$ is the level of uncertainty for this drug, and ΔX_j is the change in market factor structure from the first year to t years after marketing. φ captures the level of price change for drugs with no uncertainty and no change in market structure. The problem here is that the level of uncertainty is not observable. To identify the effect of uncertainty on price changes, we use two independent types of information: the therapeutic novelty of the drug and the time span between the drug approval date in the USA and listing date in public drug plans.

Consumers (physicians and patients) learn the effectiveness of a drug through experimentation; physicians learn about the right match between a new drug and their heterogeneous patients' conditions, and patients find out if the new drug is the right match for them. Demand uncertainty is associated with the degree of a drug's novelty. Pioneer drugs, which may represent the first medicine in a therapeutic class, are more uncertain because of the lack of patient experience with this drug or others with a similar mode of action. These drugs require more extensive experimentation as patients and physicians have less information and familiarity about their effectiveness, side effects, and optimal compliance. Therefore, firms have less information about the demand parameters of more novel drugs *a priori*.

Therapeutic novelty is also associated with the number of safety warnings after approval. Olson (2004) finds that the novelty status of drugs is associated with the number of reported adverse drug reactions.[13] More novel drugs face higher safety uncertainty owing to less cumulative experience with the drug. Another factor that may contribute to uncertainty is that Health Canada accelerates the approval of Pioneer drugs with the justification of their therapeutic advantages over existing medicines. A shorter review process may result in more uncertainty about drug safety. Begosh *et al*. (2006) show that priority review drugs tend to have more black box warnings than nonpriority review drugs in the US market. This evidence suggests that therapeutic novelty is positively correlated with the level of safety uncertainty. Other new, but not Pioneer, drugs are deemed to be equivalent to existing therapies. As such, they are less uncertain as consumers have already accumulated experience with their existing substitutes in the market.

Because many drugs enter the Canadian market long after their introduction in other markets, even drugs that have Pioneer status could have a lengthy history with patients before arriving in Canada. Lasser *et al*. (2002) found that recently approved drugs are more likely to be tagged with safety warnings, and the probability of a new safety warning decreases as the drug ages. Therefore, the time lag from marketing approval in other countries until listing in Canadian public drug plans would reduce the probability of getting an unexpected quality shock.

Moreover, demand uncertainty studies show that demand parameters are learned as patients and physicians gain experience with the drug over the first few years. This information is not specific to a market and can be exploited in other markets. Therefore, the time lag from

[13] Adverse drug reactions are typically reported by health professionals when patients experience adverse health effects while taking the prescribed dosage of medicines.

marketing approval in other countries until coverage by Canadian public drug plans would reduce demand uncertainty. We classify a drug as having "US experience" if the time elapsed between the approval of the drug by the US regulatory authority (the FDA) and listing by Canadian public drug plans is 2 years or more to capture the information accumulation about the demand of a drug from US consumers' experience.

We thus have two mechanisms to identify the effect of uncertainty on price: therapeutic novelty and US experience. We also consider the interaction factor of the novelty status and the drug's US experience. Suppose D_g, a set of dummies, is equal to 1 when a drug's therapeutic novelty is equal to $g\ (= 0, 1, \dots, G)$ and is equal to zero when otherwise. D_e represents a set of dummies being equal to 1 for drugs with a given level of US experience and zero otherwise:

$$\Delta P_{jge} = \varphi + \sum_{g=0}^{G} \sum_{e=0}^{1} \delta_{ge} D_g D_e + \Delta X_{jge}\beta + \varepsilon_{jge} \qquad (2.14)$$

where ΔP_{jge} is the price change of drug j belonging to therapeutic novelty group g and experience cohort of e. ΔX_{jge} are market structure factors for each drug. φ is the common price change between all groups of drugs. δ_{ge} are the price changes specific to experience cohort e with the therapeutic group g. We use Equation 1.14 to estimate price changes from the first year to the third, fourth, fifth, and sixth year.

2.5.2 Data[14]

Sales data are drawn from the PharmaStat database of Brogan Inc. [15] This database contains information from public drug plans on the annual number of units sold, the unit price, the

[14] Data in this chapter includes 6 therapeutic classes: Cardiovascular system, Antineoplastics and immunomodulating agents, Nervous system, Anti-infective agents, Anti-diabetic and Gastrointestinal drugs. These therapeutic classes constitute around 70% of Canadian patented drug sales in 2010 (Patented Medicine Prices Review Baord, 2010).

producer, and therapeutic class to which the drug belongs.[16] Since this dataset is at the DIN level, it contains different dosage forms of a molecule; for instance, Novartis introduced Diovan, a drug prescribed for blood pressure, in the Canadian market under two doses of 80MG and 160MG. These are each treated as a unique observation.

The primary estimates are performed on new, patented drugs. Our data initially contained 293 DINs of patented drugs approved by Health Canada and listed in public plans between 2000 and 2009. We exclude 102 DINs for two reasons. First, 61 DINs are excluded from the dataset since they are not in solid form, as Brogan does not guarantee the accuracy of sales of drugs not in solid dosage form. Second, 41 DINs are excluded since their average sales between the introductory year and 2009 are less than $100,000. As a result, 191 DINs are included in this study for estimation analysis.

Prices considered in this study are the prices reimbursed by the public plans. Such prices are at the wholesale level, which includes wholesaler markups. We present data and regressions in this chapter using current prices (i.e. without any adjustment for inflation). Regressions using real prices, after adjusting by the Consumer Price Index, are almost identical. The preference for nominal prices is motivated by the nominal price-cap imposed by the provinces (i.e. zero price increases). The number of units dispensed reflects the number of tablets or capsules.

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[15] The data were supplied through an arrangement courtesy of Alberta Health and Wellness. Brogan has now merged with IMS Health Canada.

[16] PharmaStat covers all sales under public drug plans and a large percentage of private plans (around 67%) in nine provinces: British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Québec, New Brunswick, Nova Scotia, Newfoundland and Labrador. It also includes the sale of drugs under Non-Insured Health Benefits (NIHB). NIHB is a prescription drug plan whose beneficiaries are mainly aboriginal Canadians.

Health Canada's classification of drugs is used to proxy uncertainty. As Health Canada classifies newly patented drugs into different categories, our ranking of uncertainty proceeds according to the following:

- Pioneer: The most uncertain products are new molecules ranked as priority review. Health Canada offers priority review to new drug submissions for which there is substantial evidence of clinical effectiveness that the drug addresses an unmet need or achieves a significant increase in efficacy or safety.
- Me-too: We use this term to indicate new molecules without priority review. These drugs are typically similar to existing therapies and will generally have a similar or identical means of action, with a risk profile similar to the Pioneer drug in the class.
- Reformulation: New formulations typically have somewhat less uncertainty. For example, a new formulation combining two older drugs faces only the uncertainty of whether it can convince physicians that the new combination is superior to either or both of the Old drugs prescribed separately.
- Old: These drugs form a baseline, from which we compare others. Rather than using all existing drugs, we use new dosage forms of patented drugs as the benchmark. These "Old" drugs are likely to have very little uncertainty connected with them but are "new" given their revised dosage forms and their new drug information number ("DIN").

To define whether there is experience of the drug in the USA before it is listed in Canadian public drug plans, we extracted approval dates from the US Food and Drug Administration website and listing dates from PharmaStat database. If the FDA approves a drug

two or more years before being listed in Canadian public drug plans, we define this drug as having "experience" in the US market.

We included competition indicators relating to the number of drugs in the therapeutic class and the number of those drugs in generic form. To construct the competition indicators, we used a larger data set consisting of all drugs, including Older drugs, unpatented drugs, non-solid drugs, and small volume products. This larger data set consisted of 5275 DINs. Standard therapeutic classification organizes drugs into different classes according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. The *Therapeutic Class* in the PharmaStat database is generated by combining two standard classifications: ATC and AHFS[17]. The 191 new DINs considered in this chapter belong to 42 therapeutic classes. This classification was used to define substitute drugs.

2.5.3 Empirical Model

To investigate how prices are changing over time, we specify the following difference in difference regression equation:

$$\begin{aligned} LRelative_{ij}(t) &= \beta_0 + \beta_1 Pioneer_j * D_{NOX,j} + \beta_2 Pioneer_j * D_{USX,j} \\ &+ \beta_3 Metoo_j * D_{NOX,j} + \beta_4 Metoo_j * D_{USX,j} \\ &+ \beta_5 Reformulation_j * D_{NOX,j} + \beta_6 Reformulation_j \\ &* D_{USX,j} + \beta_7 Old_j * D_{NOX,j} + \beta_8 \Delta NUMB_j(t) \\ &+ \beta_9 \Delta shareGEN_j(t) + \beta_{10} LQshare_j + \varepsilon_{ij} \end{aligned} \tag{2.15}$$

[17] The Anatomical Therapeutic Chemical (ATC) Classification System is provided by the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOCC). The American Society of Health-System Pharmacists publishes the American Hospital Formulary Service (AHFS) classification. Brogan takes ATC as its primary classification with AHFS used to fill any gaps.

$LRelative_{ij}(t)$ is the logarithm of the ratio of the price of a new drug in year *t* to its launch price, where i indexes the DIN, and j indexes the jth trade name.[18] $LQshare_{j2}$ is the logarithm of the market share (in terms of pill quantity) of drug j in its therapeutic class during the second year of marketing. Because the sales data are annual and it is possible that a DIN enters the market in the middle of the year, we used the share in the second year rather than in the first year.

$Pioneer_j, Me-too_j, Reformulation_j$, and Old_j are dummy variables for drugs with various levels of uncertainty.

$D_{NOX,j}$ is a dummy variable equal to 1 for all drugs with US experience less than or equal to 2 years when listed by public drug plans and zero when otherwise. $D_{USX,j}$ equals 1 for drugs with US experience of more than 2 years when listed and zero otherwise. We explored alternate cutoffs for this dummy at 3 and 4 years of US experience. The estimation results were qualitatively unchanged. Note that the benchmark group is Old drugs with more than 2 years of US experience when listed in Canada.

$\Delta NUMB_j(t)$ is the change in the number of branded substitute drugs in a therapeutic class from year 1 to year t.[19] Notably, this number is not the number of substitute DINs: The number of substitutes is calculated based on the number of different drugs in the class. $\Delta shareGEN_j(t)$ is the change in a therapeutic class in the share of branded drugs with generic rivals from year 1 to year t. Because branded drugs with generic rivals are generally not

[18] Mathematically, $LRelative(t) = \log(\frac{p_1}{p_2})$ where p_t is the nominal price at time t.

[19] $\Delta NUMB(t) = NUMB(t) - NUMB(1)$.

supported by investment in promotion to physicians, such branded drugs become weaker competitors. Previous studies also treat these two types differently.

It should be noted that all regressions in this chapter are conducted by treating different dosage forms of a patented drug as a cluster. Price trends of different dosage forms of a drug are more similar to each other than those of other drugs, and there is likely to be a correlation between error terms within clusters. Using cluster-robust standard errors mitigates this problem.

2.5.4 Summary statistics

Table 2.1 shows summary statistics for new DINs entering the Canadian market between 2000 and 2009. As predicted by the model, the average price decreases more, the higher the level of uncertainty. Drugs classified as Pioneers and Me-toos, on average, experienced a 4% price decrease in the 4 years after launch, while the mean fall in prices for $reformulations$ is only 1%, and old drug prices, on average, rise 1%.

Figure 2.1: Distribution of current price changes in the first 4 years also depicts the distributions of price changes in the first 4 years of marketing for different groups of DINs. While some DINs in the Pioneer and Me-too groups experience extensive price reductions, the price changes for Reformulations and Old drugs are more or less in the same range. Even after eliminating the outlier DINs, the average price decreases for Pioneers are larger than those for other groups. This shows that the primary inference is consistent with the theory presented previously, as more uncertain drugs tend to decrease their prices more than other groups, on average.

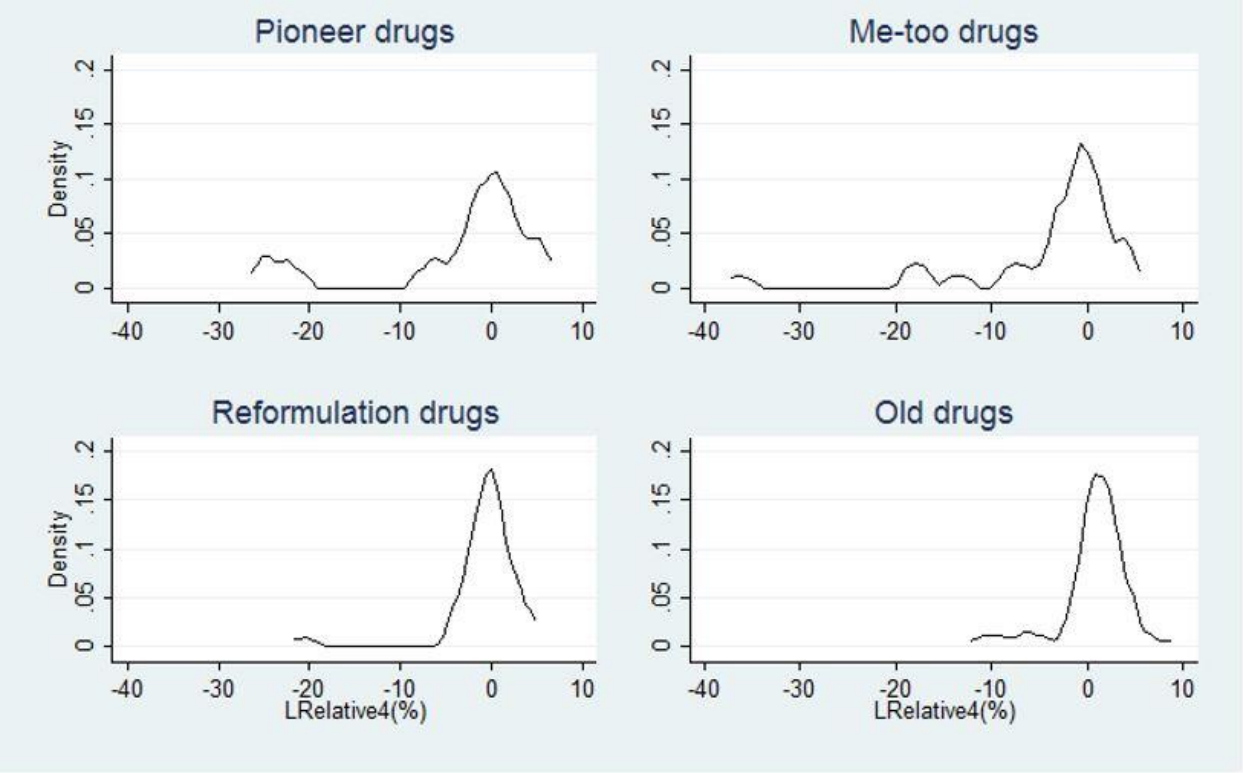

Figure 2.1: Distribution of current price changes in the first 4 years

The second row in Table 2.2 shows summary statistics for the share of molecules in a therapeutic class in their second year of marketing. There is no systematic difference in the mean quantity share in the second year among groups. While the quantity shares of Pioneer and Reformulation drugs are, on average, greater than 20%, this number for Me-too and Old drugs is almost 16%. The last two rows of Table 2.1 show the change in the number of brand substitute drugs and the share of brand substitute drugs with generic rivals. Pioneer drugs tend to see more entry in their therapeutic class, with an average of 1.89 entrants in the first four years after approval. However, this number for Me-too and Reformulation drugs is 0.89 and 0.95 respectively. Old drugs experience the entry of 1.62 competitors in the first four years of marketing. The change in the number of branded substitutes with generic rival is less volatile. This share for Pioneer drugs decreases as they experience the entry of newly patented drugs

more than the entry of new generics for existing branded drugs. On the other hand, drugs in other groups encounter more branded substitutes with generic rivals.

Table 2.1: Summary statistics for four types of drugs*

Variables	Pioneer			Me-too			Reformulation			Old drugs		
	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
LRelative4	19	-0.04	0.09	28	-0.04	0.09	38	-0.01	0.04	54	0.01	0.03
Qshare2	19	28.02	40.65	28	15.99	32.10	38	22.75	38.29	54	16.40	23.20
ΔNUMB(4)	19	1.89	1.59	28	0.89	0.88	38	0.95	1.67	54	1.62	1.27
ΔshareGEN(4)	19	-0.02	0.03	28	0.10	0.20	38	0.09	0.24	54	0.07	0.15

* LRelative4 is defined as the logarithm of the ratio of the price of a new drug in 4 years from lunch to its lunch price. Qshare2 is the market share (in terms of pill quantity). ΔNUMB(4) is defined as the change in the number of branded substitute drugs in a therapeutic class from year 1 to year 4. ΔshareGEN(4) represents the change in a therapeutic class in the share of branded drugs with generic rivals from year 1 to year 4.

2.6 Results

All estimation results are reported for different durations (3, 4, 5, and 6 years)[20] after the introductory year. Using different durations enables us to investigate the effect of the explanatory variables on the pricing behaviour of firms at varying points after launch. Although the price data consists of a panel, we use ordinary least squares on the difference in prices from introduction to *t* years following introduction. This approach is appropriate since our measures of uncertainty are constant for each drug, and not time-varying.

Table 2.2 reports the estimation results for equations having only therapeutic novelty indicators. We start the interpretation of results by exploring the coefficients for therapeutic novelty indicators in the fourth-year estimation (column 2). The prices for Pioneer and Me-too drugs tend to fall faster than DINs in other groups. Column 2 shows that the total price decrease

[20] As mentioned before, the data are annual, and it is possible that a drug (DIN) enters into the market at the end of the year. The second year estimation is not included to make sure that firms have had enough time to get feedback from the market and adjust the price in response to this new information.

in the first 4 years of marketing for these DINs is, on average, 4.4% more than Old DINs, while this number for Reformulation DINs is 1%. The coefficients for Pioneer and Me-too DINs are significant at the 5 and 10% level, respectively, while the coefficient for Reformulation DINs is not significant. It should be noted that the intercept reflects the rate of price changes for Old DINs because these drugs are considered as the benchmark. These DINs experience more than 2% price increase, although this is not statistically significant.[21]

Table 2.2: Price changes and therapeutic novelty indicators

VARIABLES	(1) LRelative3	(2) LRelative4	(3) LRelative5	(4) LRelative6
Pioneer	-0.021	-0.044*	-0.048*	-0.052*
	(0.023)	(0.024)	(0.029)	(0.028)
Me-too	-0.023	-0.044**	-0.041*	-0.049*
	(0.019)	(0.019)	(0.023)	(0.025)
Reformulation	0.004	-0.009	-0.016	0.022
	(0.015)	(0.014)	(0.023)	(0.021)
ΔNUMB(t)	0.006	0.004	0.012**	0.009*
	(0.006)	(0.005)	(0.005)	(0.005)
ΔshareGEN(t)	0.029	0.003	-0.010	-0.060
	(0.025)	(0.024)	(0.035)	(0.044)
LQshare2	0.004**	0.006**	0.008**	0.015***
	(0.002)	(0.003)	(0.003)	(0.004)
Constant	-0.002	0.023	0.023	0.051*
	(0.017)	(0.015)	(0.027)	(0.030)
Observations	145	139	129	107
R-squared	0.057	0.138	0.118	0.250

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

We now consider how the estimation results differ across time, as shown in Table 2.2. The Pioneer and Me-too indicators are significant for all periods except the third-year estimation. However, the difference between Pioneers and Me-toos is not statistically significant. The

[21] We also performed the same regressions with real prices. The results did not change, except that the intercepts, the change in the current price of Old drugs, are negative.

coefficients for Reformulation drugs are not statistically different from zero in all of estimations, indicating that Reformulation drugs are following the same price trends as Old drugs. Moreover, the prices for DINs embodying new active substances (Pioneers and Me-toos) decrease faster in the first 3 and 4 years of marketing as these coefficients in the following years remain at same level of those in the fourth-year estimation. In other words, pharmaceutical firms tend to cut the prices of novel drugs faster in the early years of marketing and then follow the general trend in the following years. The results in Table 2.3 confirm this finding as these estimation results show the price changes between the third year and the sixth year (LRelative36) and between the fourth year and the sixth year (LRelative46) as the dependent variables. The coefficients for Pioneer and Me-too are not significant in these estimations. Moreover, the magnitudes are not different from zero for Me-toos in both estimations and for Pioneers in the second one. This result suggests that the price trends follow the same path for all drugs after the fourth year of marketing. In summary, without considering the US experience of new drugs upon entry to Canada, the empirical results support the theoretical model, in that the greater the therapeutic novelty of a drug, the greater the average price decrease.

Table 2.3: Price changes between third and sixth years and fourth and sixth years

VARIABLES	(1) LRelative36	(2) LRelative46
Pioneer	-0.015	0.001
	(0.017)	(0.012)
Me-too	-0.006	-0.003
	(0.012)	(0.010)
Reformulation	0.010	0.011
	(0.012)	(0.011)
ΔNUMB(t)	0.009	0.005
	(0.007)	(0.005)
ΔshareGEN(t)	-0.077**	-0.064*
	(0.034)	(0.034)
LQshare(t)	0.008**	0.004
	(0.003)	(0.003)
Constant	0.034**	0.019
	(0.016)	(0.014)
Observations	107	107
R-squared	0.213	0.129

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Recall that the "US experience" of a drug in our regressions indicates that the drug was marketed in the USA for at least 2 years prior to being listed in Canadian public drug plans. It seems likely that the uncertainty related to a drug decreases, the greater is its US experience when it enters the Canadian market. We therefore interacted therapeutic novelty indicators and US experience dummy variables in the estimation. This specification identifies the effect of uncertainty more precisely. If uncertainty is resolved by experience in the market, then only Pioneer and Me-too drugs without US experience should have price reductions. As the literature on the safety and efficacy uncertainty of new drugs suggested, the level of demand uncertainty not only varies based on therapeutic novelty but also changes the more experience there is with the drug.

Table 2.4 reports the estimation results for Equation 2.15. The first row shows the specific price changes for Pioneer drugs without US experience. This group of Pioneer drugs experiences the largest price decreases. However, the coefficient for Pioneer drugs with US experience is approximately zero. The coefficient for Me-too drugs listed without delay is also negative and significant. The coefficient for Me-toos listed with lag is negative, although not significant. Moreover, US experience does not have any significant effect on price changes for Reformulation and Old drugs. These estimation results further support the association of price decreases and demand uncertainty.[22]

In general, drugs with high uncertainty tend to set a high price in the introductory year, relative to subsequent years. This is a rational reaction to the regulations restricting price increases in the following years, as shown in the simple model presented in section 2.4. The market exploration process for new innovative drugs should result in price decreases only after the market response is not favorable. Such an exploration strategy is followed only by Pioneer and Me-too drugs without extensive market exposure in the USA.

[22] As a robustness check, we also included the calendar year in which a given drug was entered the Canadian market in the regression. The results did not change qualitatively (Appendix 5).

Table 2.4: Price changes and the interaction of therapeutic novelty and US experience dummies

VARIABLES	(1) LRelative(3)	(2) LRelative(4)	(3) LRelative(5)	(4) LRelative(6)
Pioneer without US experience	-0.029	-0.052**	-0.056**	-0.052**
	(0.026)	(0.026)	(0.027)	(0.025)
Pioneer with US experience	0.019	0.007	0.003	-0.018
	(0.019)	(0.023)	(0.030)	(0.038)
Me-too without US experience	-0.035	-0.048**	-0.053**	-0.058**
	(0.022)	(0.021)	(0.023)	(0.025)
Me-too with US experience	-0.016	-0.038	-0.032	-0.046
	(0.027)	(0.028)	(0.032)	(0.033)
Reformulation without US experience	0.005	-0.010	-0.020	-0.002
	(0.020)	(0.017)	(0.019)	(0.023)
Reformulation with US experience	0.001	-0.009	-0.017	0.024
	(0.016)	(0.013)	(0.027)	(0.019)
Old drugs without US experience	-0.006	-0.012	-0.020	-0.000
	(0.026)	(0.024)	(0.016)	(0.021)
ΔNUMB(t)	0.006	0.004	0.011**	0.005
	(0.006)	(0.005)	(0.005)	(0.004)
ΔshareGEN(t)	0.030	0.011	-0.002	-0.039
	(0.026)	(0.020)	(0.028)	(0.031)
LQshare2	0.004*	0.005**	0.009***	0.012***
	(0.002)	(0.003)	(0.003)	(0.004)
Constant	-0.001	0.018*	0.030	0.046**
	(0.017)	(0.011)	(0.022)	(0.020)
Observations	142	136	126	104
R-squared	0.070	0.167	0.181	0.279

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

While the coefficients for the change in the number of patented substitutes are significant at the 5% level in the fifth and sixth year estimations, they are not significant for the other years as shown in Table 2.2. The coefficients for the share of branded drugs with generic rivals are not significant for any period. The surprising aspects of these coefficients are the signs. The signs for the change in the number of branded drugs are positive meaning that the entry of a newly patented substitute is associated with an increase in the prices of existing drugs by roughly 1% by the fifth or sixth year of the original drug. While the result is not strong, it is consistent with a

situation in which drugs with revealed high demand attract other firms to enter the category with Me-too drugs.

Another competitive aspect of firms' behaviour is realized in the coefficients of the quantity share of drugs in the second year. These coefficients are significant for all estimations with a positive sign. The positive sign indicates that drugs starting with a larger share, on average, are less likely to decrease their prices in the following years. However, the magnitudes of these coefficients are very small.

It is important to consider why, in the specific context of the Canadian market, a firm would find it profit-maximizing to lower the price of a product which had had a poor realization of quality uncertainty. Our data is drawn from Canadian public plans, so it is not obvious how, for insured patients, price affects quantity. However, while patient demand is likely relatively inelastic, the same is not necessarily true for drug plans. For a drug with low realized quality, in order to become insured in additional provinces, the firm may need to lower the drugs price; similarly, in order to avoid delisting in provinces where the drug is already insured, a price decrease may be required.

2.7 Conclusion

This chapter examines the pricing strategies of pharmaceutical firms in a regulated market with upward price rigidity. The level of uncertainty associated with a drug is found to be a crucial determinant of price evolution in the Canadian pharmaceutical market. Given that the established price in the introductory year is the highest achievable price in the drug's life cycle in a regulated market with upward price rigidity, drugs facing uncertainty in their market reception tend to start with a high introductory price. Pharmaceutical firms will adjust their prices if the market reception is unfavourable. Such an exploration strategy is followed only by young innovative

drugs because the Old ones are exposed to less uncertainty. The simple theoretical model shows that this behaviour is the profit-maximizing reaction to the Canadian pharmaceutical market environment.

Appendices

Appendix 2.1: Optimization problem in the regulated market

The optimization problem for the firm in the regulated market is:

$$\max_{p_1,p_{2h},p_{2l}} \pi = \big(\alpha - \beta p_1 + \gamma E(q)\big)p_1 + \delta[(1-\lambda)(\alpha - \beta p_{2l} + \gamma q_l)p_{2l} + \lambda(\alpha - \beta p_{2h} + \gamma q_h)p_{2h}]$$

$$s.t.\ \ p_{2h} \le p_1$$

This optimization can be written as:

$$\max_{p_1,p_{2l}} \pi = \big(\alpha - \beta p_1 + \gamma E(q)\big)p_1 + \delta[(1-\lambda)(\alpha - \beta p_{2l} + \gamma q_l)p_{2l} + \lambda(\alpha - \beta p_1 + \gamma q_h)p_1]$$

The first order condition for $p_1\ and\ p_{2l}$ is as follows:

FOC for p_1:

$$\frac{\partial \pi}{\partial p_1}: \alpha - 2\beta p_1 + \gamma E(q) + \delta\lambda(\alpha - \beta p_1 + \gamma q_h) = 0$$

$$=> \alpha(1+\delta\lambda) - 2\beta p_1(1+\delta\lambda) + \gamma E(q) + \delta\lambda\gamma E(q) - \delta\lambda\gamma E(q) + \delta\lambda\gamma q_h = 0$$

$$=> \alpha(1+\delta\lambda) - 2\beta p_1(1+\delta\lambda) + \gamma E(q)(1+\delta\lambda) + \delta\lambda\gamma(1-\lambda)(q_h - q_l) = 0$$

$$=> p_1 = \frac{\alpha + \gamma E(q)}{2\beta} + \frac{\delta\lambda\gamma(1-\lambda)(q_h - q_l)}{2\beta(1+\delta\lambda)}$$

FOC for p_{2l}:

$$\frac{\partial \pi}{\partial p_{2l}}: \delta(1-\lambda)(\alpha - 2\beta p_{2l} + \gamma q_l) = 0$$

$$=> p_{2l} = \frac{\alpha + \gamma q_l}{2\beta}$$

Appendix 2.2: Welfare Analysis

Total welfare for a market with a linear demand function of $x_t = \alpha - \beta p_t + \gamma q_t$ and a firm with zero marginal cost is as follows:

$$W_t = \pi_t + CS_t$$

$$\pi_t = x_t * p_t$$

$$CS_t = \frac{1}{2}(p_t^0 - p_t) * x_t$$

p_t^0 is price where quantity demanded is zero while $x_t \; and \; p_t$ are the optimal price and quantity.

Total welfare in the unregulated market:

The total welfare with the general demand function is:

$$W_t = \frac{1}{\beta}\left(\frac{\alpha + \gamma q_t}{2}\right)^2 + \frac{1}{2\beta}\left(\frac{\alpha + \gamma q_t}{2}\right)^2 = \frac{3}{2\beta}\left(\frac{\alpha + \gamma q_t}{2}\right)^2$$

By applying the measure of qualities in each period (expected quality in the first period and realization of high and low quality in the second period) and the weights (discount factor for the second period and probability of high and low quality realization), the total welfare in the unregulated market is as follows:

$$W^U = \frac{3}{2\beta}\left[\left(\frac{\alpha + \gamma E(q)}{2}\right)^2 + \delta\lambda\left(\frac{\alpha + \gamma q_h}{2}\right)^2 + \delta(1-\lambda)\left(\frac{\alpha + \gamma q_l}{2}\right)^2\right]$$

Total welfare in the regulated market:

Upward price-rigidity resulting from the price regulation distorts the firms' optimal choices in the first period and for the realization of high quality in the second period, but not for the realization of low quality in the second period. The optimal price, quantity and price where the quantity demanded is zero are listed in following table:

Variables	Unregulated Market	Price where quantity demanded is zero
p_1	$\frac{\alpha+\gamma E(q)}{2\beta}+\frac{\delta\lambda\gamma(1-\lambda)(q_h-q_l)}{2\beta(1+\delta\lambda)}$	$\frac{\alpha+\gamma E(q)}{\beta}$
p_{2h}	$\frac{\alpha+\gamma E(q)}{2\beta}+\frac{\delta\lambda\gamma(1-\lambda)(q_h-q_l)}{2\beta(1+\delta\lambda)}$	$\frac{\alpha+\gamma q_h}{\beta}$
p_{2l}	$\frac{\alpha+\gamma q_l}{2\beta}$	$\frac{\alpha+\gamma q_l}{\beta}$
x_1	$\frac{\alpha+\gamma E(q)}{2}-\frac{\delta\lambda\gamma(1-\lambda)(q_h-q_l)}{2(1+\delta\lambda)}$	-
x_{2h}	$\frac{\alpha+\gamma E(q)}{2}-\frac{\gamma(1-\lambda)(q_h-q_l)}{2(1+\delta\lambda)}$	-
x_{2l}	$\frac{\alpha+\gamma q_l}{2}$	-

Total welfare is calculated by using the values from the above table to the welfare function as:

$$W^R=\frac{3}{2\beta}\left[\left(\frac{\alpha+\gamma E(q)}{2}\right)^2+\delta\lambda\left(\frac{\alpha+\gamma q_h}{2}\right)^2+\delta(1-\lambda)\left(\frac{\alpha+\gamma q_l}{2}\right)^2\right]$$

$$+\left(\frac{\delta\lambda(1+\delta\lambda)}{2\beta}\right)\left(\frac{\gamma(1-\lambda)(q_h-q_l)}{2(1+\delta\lambda)}\right)^2$$

Appendix 2.3: Robustness Check

As a further robustness check, we added dummy variables for the calendar year in which a given drug was introduced. It is possible that drugs entering the market in different years follow a similar pattern. However, the inclusion of such dummy variables did not change the general results for the interaction of product novelty indicators and US experience dummies.

Table A.2.3 – Estimation Results with Dummies for the Introduction Years

	(1)	(2)	(3)	(4)
VARIABLES	LRelative(3)	LRelative(4)	LRelative(5)	LRelative(6)
Pioneer without US experience	-0.012	-0.039**	-0.048**	-0.036**
	(0.021)	(0.018)	(0.020)	(0.016)
Pioneer with US experience	0.032	0.014	0.003	-0.010
	(0.021)	(0.024)	(0.035)	(0.022)
Me-too without US experience	-0.036**	-0.045**	-0.053**	-0.055***
	(0.018)	(0.018)	(0.022)	(0.021)
Me-too with US experience	-0.002	-0.019	-0.018	-0.032
	(0.029)	(0.031)	(0.033)	(0.034)
Reformulation without US	0.010	-0.009	-0.017	-0.003
experience	(0.018)	(0.019)	(0.022)	(0.024)
Reformulation with US	0.014	0.003	-0.003	0.033
experience	(0.021)	(0.018)	(0.028)	(0.020)
Old drugs without US	0.017	0.002	-0.008	0.013
experience	(0.032)	(0.032)	(0.022)	(0.032)
ΔNUMB(t)	0.006	0.005	0.011**	0.004
	(0.006)	(0.004)	(0.005)	(0.004)
ΔshareGEN(t)	0.006	-0.012	-0.010	-0.051**
	(0.022)	(0.021)	(0.029)	(0.025)
LQshare2	0.006***	0.006**	0.010***	0.013***
	(0.002)	(0.003)	(0.003)	(0.004)
D2002	-0.078***			
	(0.024)			
D2003	-0.049**	-0.042**		
	(0.024)	(0.019)		
D2004	-0.001	-0.018	-0.022	
	(0.018)	(0.024)	(0.020)	
D2005	-0.010	0.028	-0.002	-0.061***
	(0.012)	(0.019)	(0.025)	(0.015)
D2006	-0.014	0.013	0.037	-0.038
	(0.013)	(0.014)	(0.025)	(0.025)
D2007	-0.033**	0.020	0.021	0.013
	(0.013)	(0.016)	(0.019)	(0.023)
D2008	-0.037**	-0.004	0.048**	-0.009
	(0.017)	(0.017)	(0.020)	(0.022)
Constant	0.035*	0.021	0.023	0.070***
	(0.019)	(0.017)	(0.028)	(0.024)
Observations	142	136	126	104
R-squared	0.206	0.277	0.251	0.390

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Chapter Three: Delays in the Submission of New Drugs in Canada

With Aidan Hollis[23]

3.1 Introduction

Some commentators have claimed that Health Canada's process for approving new drugs is excessively slow, thereby delaying access to these drugs by Canadians (Rovere & Skinner, 2012). However, the submission of new drugs to Health Canada for approval is systematically delayed compared with submissions to regulatory agencies in the United States and the European Union, which delays the availability of new drugs in Canada. In this paper, we analyze the timing of approvals and submissions in Canada and explore possible reasons for delays based on available data. We also explore the likely effects of a harmonized process for submissions between the US Food and Drug Administration (FDA) and Health Canada.

We began our analysis by searching the drug databases of the FDA, the European Medicines Agency and Health Canada to obtain information about drugs with new molecular entities or new active substances that were approved by at least one of these agencies between 2000 and 2011. We found that differences across jurisdictions in approval-processing times played a small role in the delays. However, differences in the timing of drug submissions were an important factor. Although the mean time to approval was about 90 days longer in Canada than in the US or the EU, the mean submission delay in Canada was much longer than in the other two jurisdictions. The mean submission delay hides considerable variation: many drugs

[23] A short version of this chapter is published in Canadian Medical Association Journal: Shajarizadeh, A., & Hollis, A. (2015). Delays in the submission of new drugs in Canada. *Canadian Medical Association Journal*, *187*(1), E47-E51.

were submitted to Health Canada with no substantial delay, but others were delayed by more than two years. New drugs reached the market much later in Canada than in the US and the EU because of long delays before their submission to Health Canada. In the US and EU, most new drugs were submitted within three months after their first submission to any of the three jurisdictions. In Canada, about 70% of the new drugs were submitted more than three months, and 40% more than one year, after their first submission. For drugs that were ultimately approved in Canada and in at least one of the other jurisdictions, the mean delay from first submission in either foreign jurisdiction to submission in Canada was 540 days.

We also examine in this paper several different possible reasons for delays in submission of new drug files. Since the situation of each drug is different, there are of course different reasons for delaying (or not delaying) submission to Health Canada. Each jurisdiction varies in many respects in terms of the health system, insurance, and regulatory approach. Our technique for identifying how differences across jurisdictions affect submission delay is to exploit differences between drug categories and pharmaceutical companies. This approach allows us offer some evidence on which explanations are important, which in turn has implications for the likely effects of harmonization of the regulatory process between the FDA and Health Canada. We find that corporate capacity and priority status of new drugs are important determinants of submission delay.

3.2 Data

We obtained information about drugs with "New Molecular Entities" or "New Active Substances" approved by the US Food and Drug Administration[24] (FDA), the European Medicines Agency[25] (EMA), or Health Canada[26]. We confined our sample to the drugs approved by at least one of Health Canada, FDA, and EMA between 2000 and 2011. This sample contains 455 new drugs, of which we dropped 75 because the submission dates were unavailable. The remaining sample contains 380 drugs with the distribution of approvals as shown in Figure 3.1. This sample includes a subset of 111 drugs submitted to the FDA or the European Medicines Agency that were not submitted for approval to Health Canada. Hence, the approval of the 111 drugs in Canada would be infinitely delayed. Since our analysis does not include these drugs, the reported submission delay for Canada is biased downwards. Because we focused our analysis on the reasons for delay in Canada, we analyzed data only for the 259 drugs that were submitted to Health Canada and to at least one of the other two agencies.

[24] U.S. Food and Drug Administration, Drug information, available: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. (accessed March 27, 2013)
[25] European Medicines Agency, Human Medicines, available: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124. (accessed March 27, 2013)
[26] Health Canada, Notice of Compliance (NOC) Database, available: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/noc-acc/noc_acc_data_extract-eng.php (accessed March 27, 2013). In some case the NOC database lacked the information and submission dates were kindly provided by Health Canada.

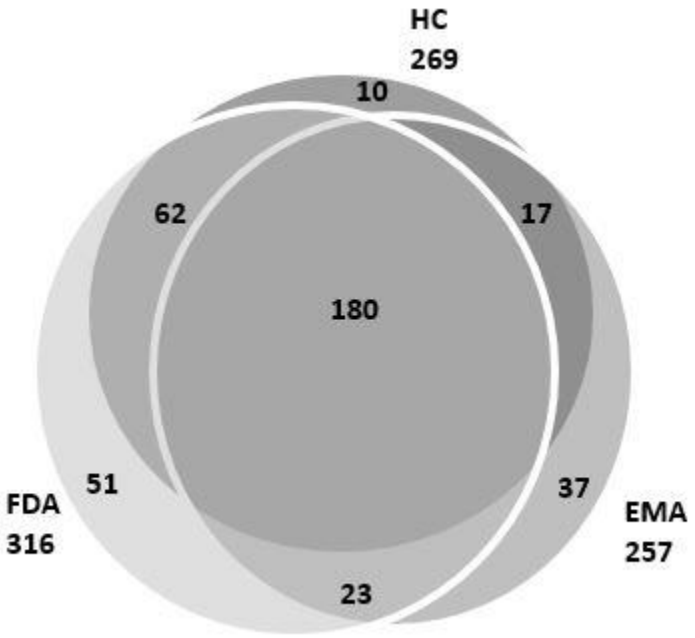

Figure 3.1: Number of drug approvals by Health Canada (HC), the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) between 2000 and 2011

Submission delay is defined as the number of days between a drug's first submission to any of the three regulatory agencies and submission in a specific jurisdiction. Thus, at least one jurisdiction has a delay of zero. Our definition of the submission date to each country is the date the sponsor submitted a complete application to the corresponding regulatory agency. The approval date is the date that the sponsor is authorized to launch the new drug in the market. The time between the submission date and the approval date is the time to approval for each jurisdiction.

Table 3.1 shows summary statistics of submission delay and time to approval for all drugs approved in Canada and at least one other jurisdiction. While average approval times are about 90 days slower for Health Canada than FDA and EMA, the average submission delay to Health Canada is much longer. The mean submission delay hides considerable variation: many

drugs are submitted to Health Canada with no significant delay, while others are delayed by more than 2 years. Figure 3.2 shows the distribution of submission delay in the three markets. The US and EU experience the majority of submissions within 3 months from the first submission. Around 70% of drugs are submitted to Health Canada more than 3 months later than the first submission and 40% of them more than 1 year.

Table 3.1: Submission delays and times to approval for new drugs submitted for approval in Canada and at least one other jurisdiction

		Submission Delay*			Time to approval+		
Country	No. of drugs	Mean	Median	SD×	Mean	Median	SD
Canada	259	540	180	810	551	442	344
United States	242	106	0	462	461	308	339
European Union	197	215	12	561	464	451	136

×SD is denoted for standard deviation.
*The interval between the date of first submission to a regulatory agency in any of the three jurisdictions and the date of submission in a specific jurisdiction.
+The interval between the submission date and the date of authorization to launch for market in each jurisdiction.

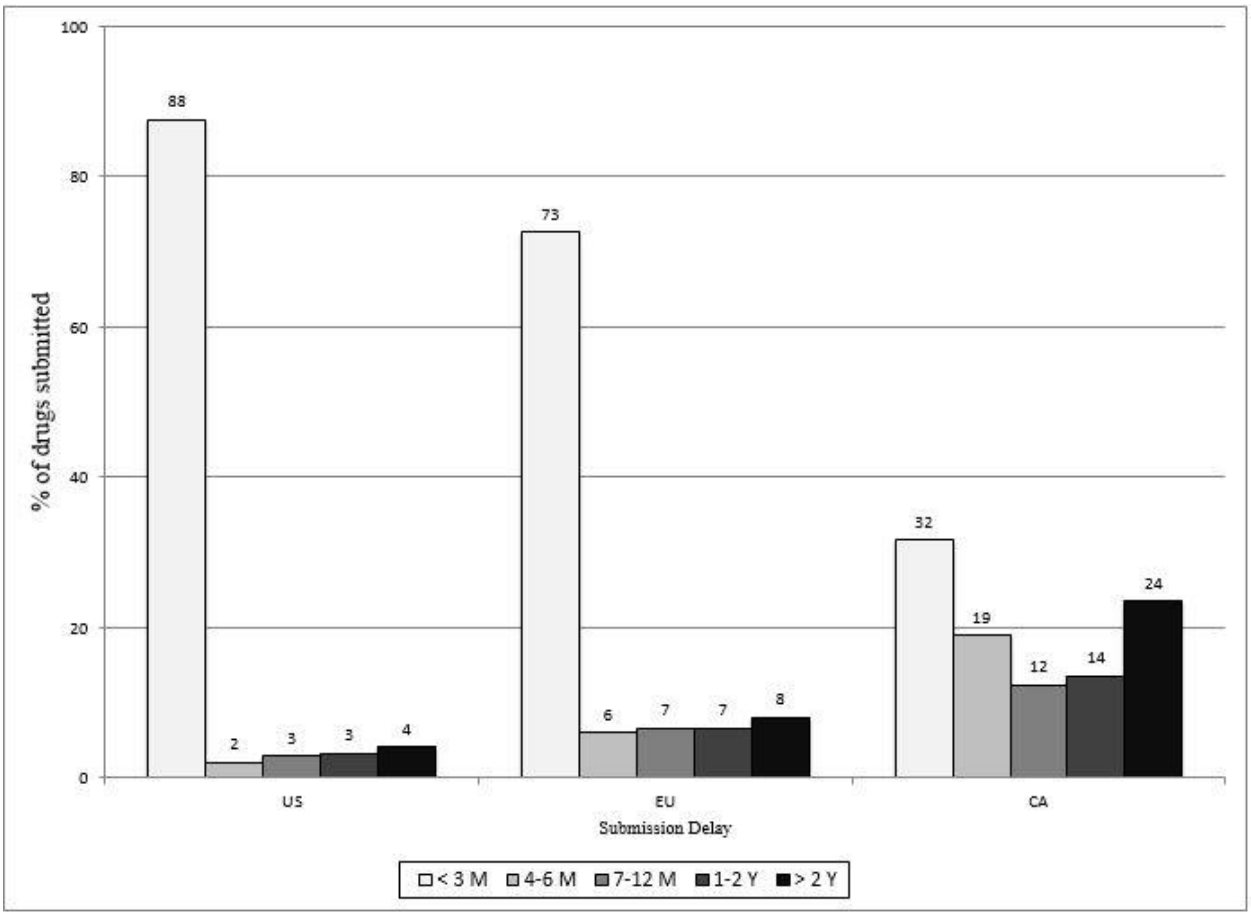

Figure 3.2: Delays in the submission of new drugs in the United States, the European Union and Canada. A submission delay is the interval between the date a drug first submitted to any of the three jurisdictions and the submission date in a specific jurisdiction

3.3 Explaining submission delays in Canada

We propose four hypotheses that may explain the delays in the submission of new drugs to Health Canada.[27] First, the data requirements for submissions may be more onerous in Canada,

[27] There are other hypothesized reasons for submission delays, some of them relating to differences in reimbursement policies across countries. The reimbursement processes in the three jurisdictions considered in this chapter is separate from the regulatory approval processes.

causing pharmaceutical companies to delay submissions. It may take longer to assemble a successful application for Health Canada than to assemble one for the FDA or the European Medicines Agency. We call this the "stringency" explanation. Second, companies may delay their submissions to Health Canada because the value of getting listed quickly in Canada is small relative to the potential harm to the regulatory process in the other jurisdictions in the event that Health Canada seeks additional information. We call this the "risk" hypothesis. Third, companies may have limited capacity to make submissions and therefore prioritize submissions by market according to profitability. Therefore, larger markets would attract the first submissions. We call this the "capacity" explanation. Fourth, companies may intentionally delay their submissions to Health Canada because they want to obtain approval for their drugs in high-priced markets first to obtain an attractive price that other countries will use as a reference. We call this the "price" explanation.

3.3.1 Stringency

We explored the stringency hypothesis by first contacting officials at Health Canada. They stated that the standards of what constitutes an adequate submission may differ for individual drugs but, on average, are roughly the same across jurisdictions for standard drugs.

The FDA offers programs that may enable early submission for new drugs for serious conditions where no acceptable treatment exists: fast-track status and accelerated approval. Fast-track status offers a rolling review in which modules of the application are submitted as they are completed. For these cases, the date of submission of the first module is considered the date of submission for the application. Accelerated approval allows firms to use surrogate outcomes that are not well-established (Field & Boat, 2011). These programs allow companies to submit what are essentially incomplete applications, which would generally not be acceptable at Health

Canada. (Health Canada is currently developing a program for orphan drugs. Consideration will be given to the small size of the patient population for the development, evaluation and approval of these drugs (Lee & Wong, 2014)) These FDA programs are heavily used for orphan drugs, as reported by Seoane-Vazquez and colleagues (2008). In 2004, the European Medicines Agency created a similar program (conditional marketing authorizations) that permits submissions for new drugs that address unmet medical needs, even when comprehensive clinical data have not been provided. However, conditional authorizations were not empirically important during the period of our analysis: as Joppi and colleagues (2009) showed, only 2 of the 44 orphan medical products approved by the European Medicines Agency between 2000 and 2007 had conditional authorizations.

To determine the extent to which the stringency hypothesis explained delays in submission to Health Canada, we analyzed our data according to whether the drugs had an orphan status in the US. We anticipated that drugs with an orphan classification in the US would have a relatively short submission delay in the US compared with the submission delays in Canada and the EU, which we expected would be similar. In general, orphan drugs were submitted much later in Canada than in the EU and the US (Figure 3.3). Many orphan drugs are never submitted to Health Canada. For those that are, it would seem advantageous to the company to submit as early as possible. We found little difference in the timing of submissions between orphan and non-orphan drugs within each jurisdiction, and a large, consistent difference between jurisdictions regardless of orphan status. We conclude that, although stringency may have had some impact on the timing of submissions, it was not a strong factor for differences in submission delays between jurisdictions.

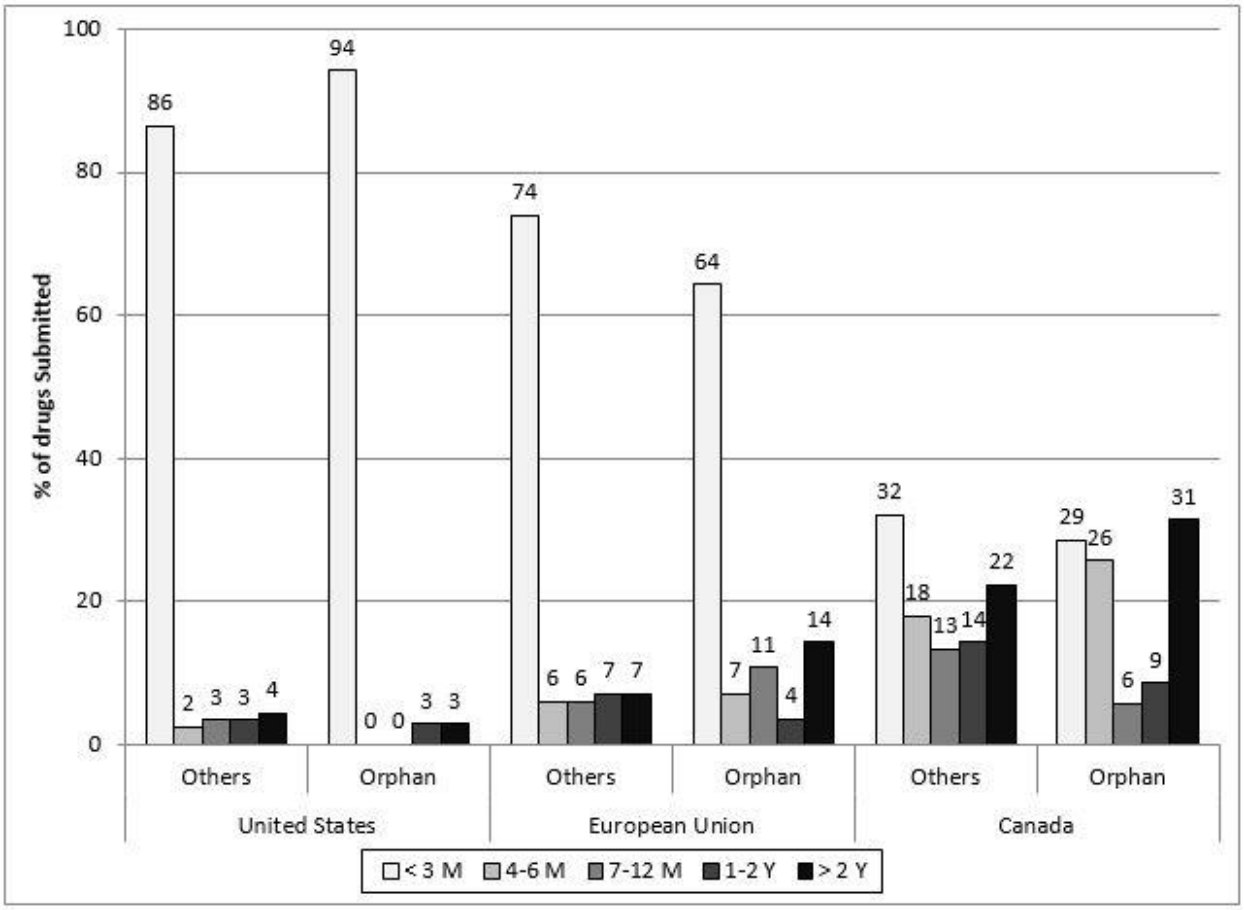

Figure 3.3: Delays in the submission of new drugs by orphan status

3.3.2 Risk

The risk that Health Canada might request additional information or the results of new studies and that such requests might have a "contagion" effect on other regulatory authorities and cause delays in the approval process in those jurisdictions could lead pharmaceutical companies to delay submission in Canada until they have gained approval for the drug in other jurisdictions. To investigate this hypothesis, we considered whether the timing of submissions in Canada was associated with marketing approval of the drugs in the US and the EU.

Of the 259 new drugs submitted to Health Canada in our sample, 88 had previously been approved in the US and 45 had been approved in the EU. Figure 3.4 shows the distribution of the time difference between approval in the US or EU and submission to Health Canada. Most of the drugs were submitted to Health Canada before they were approved in the other jurisdictions (i.e., a negative time difference). If the risk hypothesis were correct, we would expect to see a jump in the number of submissions to Health Canada at the time of approval in the other jurisdictions (time zero). Because no noticeable increase was observed (Figure 3.4), we conclude that the risk hypothesis does not explain submission delays in Canada.

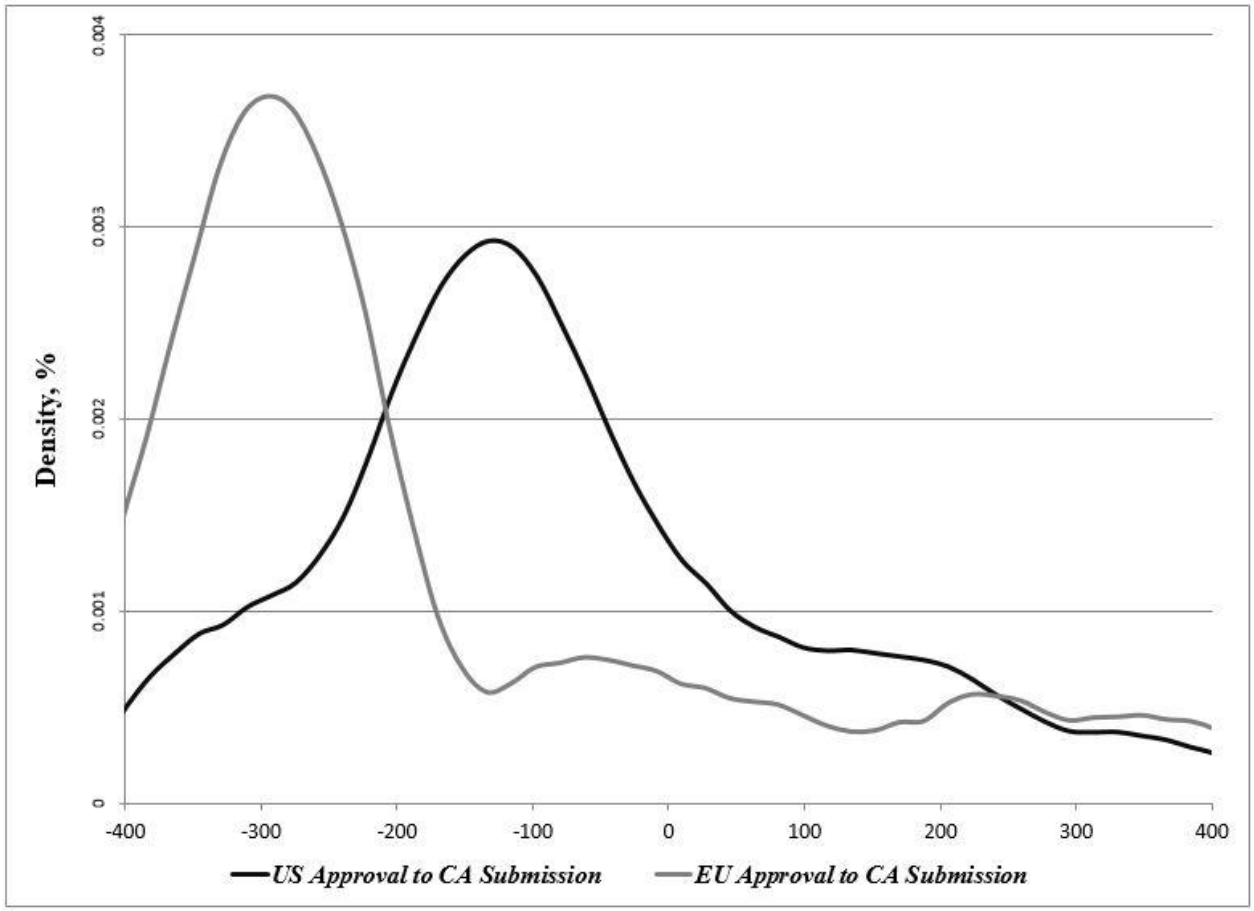

Figure 3.4: Distribution of the time difference between drug approval in the United States or European Union and submission for approval in Canada

3.3.3 Capacity

Bringing a new drug to market is costly and requires considerable expertise in the regulatory process. Health Canada's fee for submission of a new drug is $322,056 (Health Canada Health Products and Food Branch, 2014). Not all companies have the capacity inside Canada to navigate the deregulatory submission process. Larger companies are more likely than smaller ones to have dedicated staff in Canada with such expertise. Therefore, smaller companies may choose to prioritize their submissions to larger markets. To explore the capacity hypothesis, we compared submission delays by size of pharmaceutical company. Larger companies were those ranked as the top 30 in terms of sales ranked by SCRIP Intelligence (2010). Half of the 259 new drugs in our sample were marketed by these companies.

Differences in submission delays were evident between the larger and smaller companies (Figure 3.5). Applications from larger companies were 20% more likely than those from smaller companies to be submitted to Health Canada within six months after the first submission to the FDA or the European Medicines Agency. In addition, the probability of a submission delay longer than two years was 15% lower among larger companies. Although smaller companies had longer submission delays than larger companies had, this was not the entire story: submission delays were greater in Canada than in the US and EU for both large and small companies, and the difference in submission delays between Canada and the other jurisdictions was much larger than the difference between large and small companies.

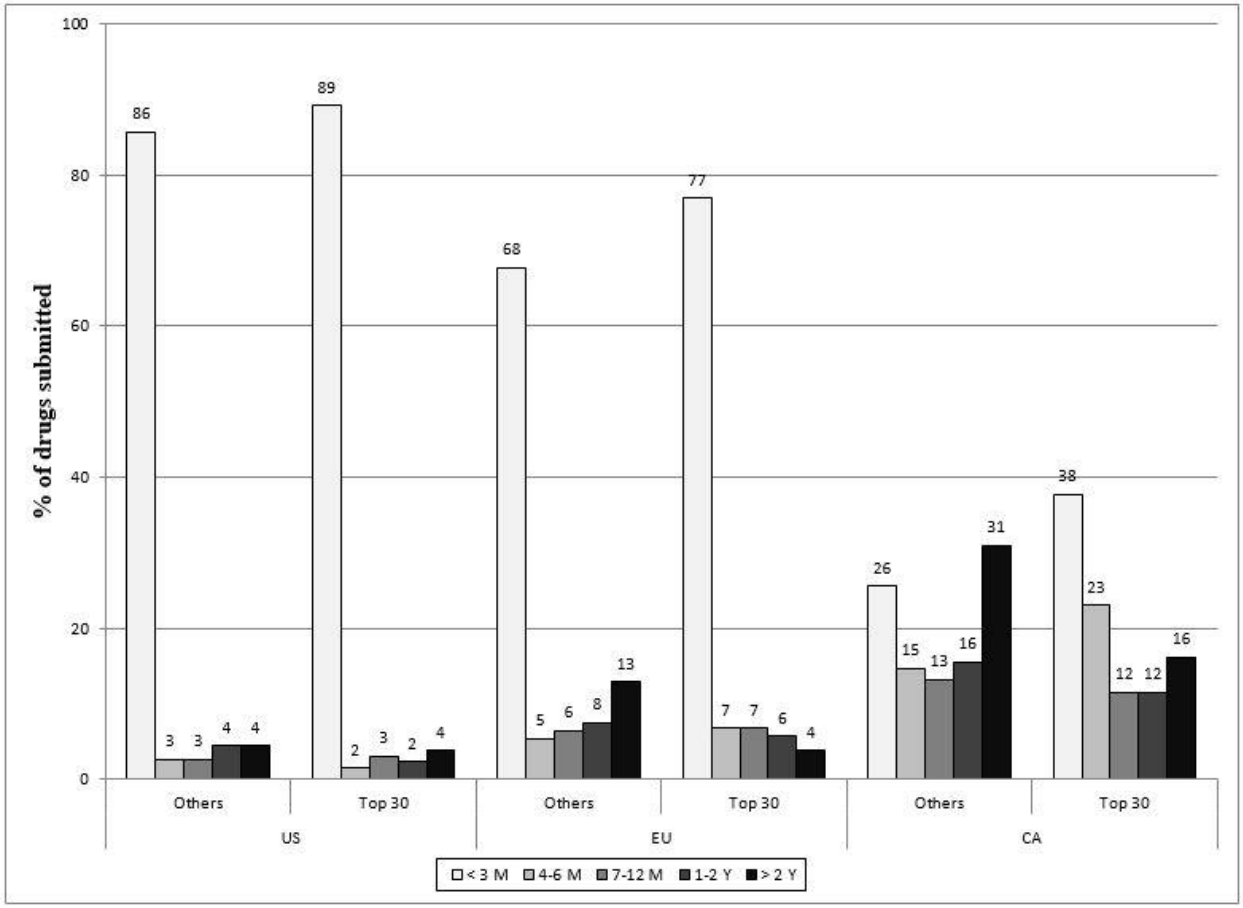

Figure 3.5: Delays in the submission of new drugs by company size. Larger companies are top 30 companies in terms of sales (ranked by Scrip Intelligence)

3.3.4 Price

Many countries consider prices in other markets when deciding what they are willing to pay for a new drug, particularly for the first drug in a class. The US is the ideal reference market if companies do in fact delay their submissions to Health Canada until they get initial approval in this higher priced market. International price referencing is important for first-in-class drugs but not as important for subsequent class entrants (i.e., me-too or follow-on drugs), because prices within a class are typically determined by the pioneer in the class in most markets, and follow-on

drugs are priced at about the same level.(Dylst, Vulto, & Simoens, 2012) This distinction is formally built into the framework for price review of Canada's Patented Medicine Prices Review Board.[28] Therefore, in our analysis of the price hypothesis, we expected first-in-class drugs to have longer submission delays than follow-on drugs in Canada.

Figure 3.6 shows the distribution of submission delays for new drugs according to their review status in Canada (priority status for first-in-class drugs and standard status for all other new drugs). Of the 259 new drugs submitted to Health Canada in our sample, 66 were recognized by the agency as having priority status. The submission delay was less than 3 months for 44% of these drugs, four to six months for 21% and seven months or longer for 36%. The submission delays in Canada for standard drugs were 27%, 18% and 55%, respectively. In effect, drugs with priority status typically were submitted to Health Canada with less of a delay than standard drugs were. Thus, we conclude that the price hypothesis does not explain the submission delays in Canada.

[28] *Compendium of policies, guidelines and procedures — reissued June 2013.* Ottawa (ON): Patented Medicine Prices Review Board; 2013. Available: www.pmprb-cepmb.gc.ca/english /View.asp?x=1733 (accessed 2013 Nov. 15).

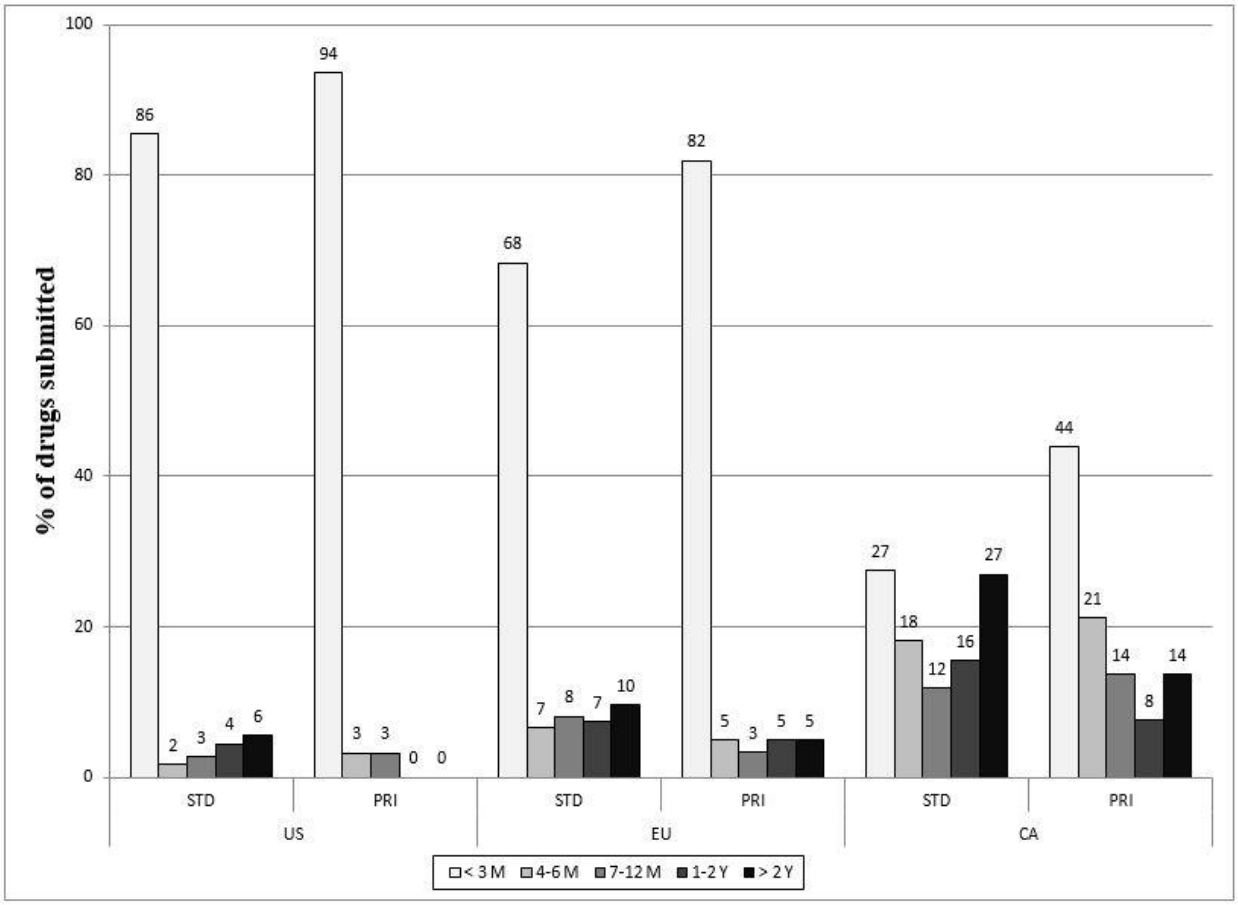

Figure 3.6: Delays in the submission of new drugs by Priority (first-in-class drugs) and Standard (all other new drugs) review status

3.3.5 Joint analysis

In this section, we provide a multivariate analysis by considering variables representing a proxy for each hypothesis. We present the results of two models in Table 3.2; first, focusing only on submission delays in Canada in columns 1 and 2, and second, including the submission delay in all three jurisdictions in columns 3 and 4. The dependent variable in this analysis is the submission delay as defined. The explanatory variables are dummies for US Orphan Status ($Orphan$), Priority Status in Canada ($Priority$), and Top 30 companies ($Top30$). Because

Priority and Orphan drugs originated by top 30 companies might have a different delay than the ones originated by small companies, we also estimate models including the interaction of the Top 30 companies dummy with the Priority Status and US Orphan Status dummies:

$$Submission - delay_i = \alpha + \beta_1 Orphan_i + \beta_2 Priority_i + \beta_3 Top30_i + \beta_4 Orphan_i * Top30_i + \beta_5 Priority_i * Top30_i + \epsilon_i \quad (3.16)$$

where drugs are denoted by subscript i. In columns 3 and 4, dummies for the EU and Canada are included, with the US being the omitted category:

$$Submission - delay_{ij} = \alpha_0 + \alpha_1 Canada_{ij} + \alpha_2 EU_{ij} + \beta_1 Orphan_{ij} + \beta_2 Priority_{ij} + \beta_3 Top30_{ij} + \beta_4 Orphan_{ij} * Top30_{ij} + \beta_5 Priority_{ij} * Top30_{ij} + \epsilon_{ij} \quad (3.17)$$

where drugs are denoted by i and jurisdictions are denoted by j. Note that in the following analysis the benchmark group is the non-orphan, standard review status drugs originated by small companies.

Drugs originated by Top 30 companies are 9 months faster in submission to Canada. This suggests that corporate capacity is a particularly important determinant of submission delays to Canada. It appears that firms do not delay submission based on orphan status, as coefficients for this variable are not significant (columns 1 and 3). Including the interaction terms as in columns 2 and 4, however, shows that for orphan drugs, the size of the originator has a substantial effect on submission timing. In Canada, orphan drugs originated by small companies were submitted 431 days (14 months) later than the benchmark group while orphan drugs originated by top 30 companies were submitted 482 days (the summation of coefficients for $Orphan$, $Top30$, and $Orphan * Top30$ in column (2)) earlier than the benchmark group. This result is consistent with

and **Error! Reference source not found.**, which show that company size, but not orphan status, i nfluences submission delay.

Table 3.2: Regression Results

	(1)	(2)	(3)	(4)
VARIABLES	Canada	Canada	3 Jurisdictions	3 Jurisdictions
Orphan Status	126	431**	74	222**
	(144)	(195)	(69)	(95)
Priority Status	-354***	-438***	-217***	-297***
	(113)	(160)	(54)	(78)
Top 30 Companies	-294***	-250**	-186***	-185***
	(98)	(117)	(47)	(57)
Orphan*Top 30 Companies	-	-663**	-	-314**
	-	(287)	-	(137)
Priority*Top 30 Companies	-	175	-	159
	-	(225)	-	(107)
The EU	-	-	119**	122**
	-	-	(60)	(60)
Canada	-	-	429***	430***
	-	-	(56)	(56)
Constant	762***	737***	251***	248***
	(77)	(83)	(50)	(53)
Observations	259	259	698	698
R-squared	0.07	0.09	0.12	0.13

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Drugs with substantial therapeutic improvement, *ceteris paribus,* are submitted to Canada with less delay (approximately one year less, as shown in column 1) and to all jurisdictions with less delay (approximately 7 months less, as shown in column 3) than follow-on drugs. This result is robust to including the interaction terms and is not dependent on company size. Since drugs with priority status are more likely to be internationally price-referenced, this suggests firms may not see international referencing as an impediment to entering the Canadian market.

Coefficients for country dummies represent, after controlling for other factors, the average submission delay to HEALTH CANADA and EMA (columns 3 and 4). The positive coefficients for both Canada and the EU illustrate that the US market is the first target of pharmaceutical companies. The coefficient for the EU dummy is around 120 days, indicating that firms submitted their application to EMA, on average, 4 months later than to the FDA. Drugs were submitted to HEALTH CANADA, on average, 14 months after being submitted to the FDA.

3.4 Canada compared with other smaller markets

In the previous sections, we compared the two largest markets in the world with Canada and found that corporate capacity appears to be an important determinant of submission delays. If this is the case, other relatively small markets would be expected to experience delays similar to Canada's. Few countries could be used for comparison because submission dates are considered confidential in most jurisdictions. We chose Australia because its Therapeutic Goods Administration (TGA) publishes public assessment reports for new reviewed drugs that contain the year of submission for a small number of drugs, mostly drugs submitted after 2007.[29] We

[29] Therapeutic Goods Administration, Australian Public Assessment Reports for prescription medicines, available: http://www.tga.gov.au/industry/pm-auspar-active.htm. (accessed Nov 15, 2013)

compare the submission year of drugs submitted to both Australia and Canada with the other two large markets.[30]

Table 3.3 shows summary statistics of submission delay for the 38 drugs submitted to both Canada and Australia. Drugs were submitted for approval to Australia after they were submitted to Canada. Because the market is somewhat smaller in Australia than in Canada, this finding supports the corporate capacity hypothesis.

Table 3.3: Submission delay for drugs submitted to Canada and Australia

Country	Obs	Mean	Median	Std. Dev.
Canada	38	0.73	0.5	0.86
Australia	38	1.08	1	1.85
United States	36	0.06	0	0.23
European Union	35	0.25	0	0.74

3.5 Discussion

Health Canada is currently working with the FDA to develop a harmonized system for new drug submissions. The harmonized system will enable companies to use the same electronic portal to submit applications to both Health Canada and the FDA, which may accelerate the approval process (Health Canada, 2012). This system will also incorporate a new pathway for the approval of orphan drugs in Canada. Although the new portal will facilitate submissions to both agencies, there is no requirement to submit to both at the same time. Therefore, if the reason for delaying a submission is a lack of global regulatory capacity, the approval process will be accelerated. Our

[30] The Australian data contains only the year of submission for a limited number of drugs. Therefore, we changed the above defined sample of drugs in two ways. First, the submission year, instead of submission date, is considered in the analysis. Second, the sample of drugs is confined to those approved in both Canada and Australia.

analysis suggests that harmonized submission for the FDA and Health Canada will accelerate the arrival of new drugs in Canada, mainly for smaller companies that appear to delay because of lower capacity for submissions.

3.6 Conclusion

We examined several possible reasons for delays in the submission of new drug applications to Health Canada, and our findings are revealing. We found that corporate capacity and priority status of new drugs are important determinants of submission delay. We believe that the harmonization of the regulatory processes of the FDA and Health Canada may accelerate drug submissions in Canada. However, because the situation is different for every drug, there may be other reasons for delaying (or not delaying) a submission to Health Canada that have not been covered in this article. Each regulatory domain varies in terms of its health care system, insurance coverage and regulatory approach. We examined differences in submission delays between orphan and non-orphan drugs and between first-in-class and follow-on drugs, but other differences may also affect the process.

Chapter Four: Value-based Pricing and Multi-Type Health Technologies

4.1 Introduction

Value-based pricing (VBP) schemes, in which the price of a health technology is linked explicitly to its health benefits, has been gaining momentum in becoming the prevalent method of price-setting for health technologies; it is extensively and explicitly used in pricing new pharmaceuticals in many countries (Paris & Belloni, 2013). It is also on the verge of being used in other segments of health care market in the US (Burwell, 2015). VBP is perceived to provide the right incentives to innovative companies to invest in the most valuable health technologies (Claxton *et al.*, 2008).

In this chapter I investigate the effect of VBP when a new technology[31] offers the potential to be used for more than one patient type. I allow for the division of patient populations to be determined *exogenously* for multi-indication technologies or *endogenously* for multi-subgroup technologies. In multi-indication technologies, the disease is clearly distinct, and so different clinical trials are required. For example, sildenafil is indicated to treat both pulmonary arterial hypertension and erectile dysfunction. In multi-subgroup technologies, patients themselves are heterogeneous in their response to treatment because of identifiable covariates such as age, lifestyle or genetic predisposition. Alternatively, the disease itself may vary in a way that requires identification for the most effective treatment. For example, acute lymphoblastic

[31] A health technology could be a pharmaceutical product, vaccine, blood product, biological compound, or medical device.

leukemia is a heterogeneous disease, including several subtypes (T-ALL, E2A-PBX1, BCR-ABL, TEL-AML1, MLL) that differ in their response to chemotherapy (Golub, 1999; Silverman, 2007; Yeoh *et al.*, 2002). In some cases, the distinction between multi-indication and multi-subgroup may be unclear.

The manufacturer decides which indications or subgroups to target and also how much information to generate, taking into account pricing schemes and the information requirement of the regulatory agencies and payers during the development process. In the case of multi-indication technologies, the manufacturer determines for which indication it will apply for approval.[32] In the case of multi-subgroup technologies, the manufacturer also has to decide whether to generate the information required to distinguish between the patient subgroups. The simple model provided in this chapter shows that some pricing schemes used by payers create distortions in targeting patient-types in the case of multi-indication technologies. The pricing schemes, on the other hand, do not affect the behaviour of the manufacturer in distinguishing subgroups. Some pricing schemes also create price distortions for existing and future health technologies for multi-indication and multi-subgroup technologies.

Health technologies increasingly come to the market for multiple patient-types; many health technologies treat more than one indication or patient subgroup and their health benefits differ substantially across their uses. In many instances, the division of a patient population into indications or patient subgroups is determined exogenously. In some disease areas, such as oncology, patients are divided by indication, and manufacturers are required to conduct clinical

[32] The case of the closely related products Avastin (indicated for certain cancers) and Lucentis (indicated for macular degeneration) is an unusual one in that in many countries Avastin is now approved for the macular degeneration use even though the manufacturer has never applied for that indication.

trials separately for each indication. For example, cancer drugs are often introduced to market for late-stage patients, and then subsequently for early-stage patients. Sometimes an existing drug could be beneficial for another therapeutic area outside the scope of the first indication. Such "indication-extension", also called "drug repositioning", has been promoted as a strategy for boosting the productivity of research and development in the pharmaceutical industry; drug repositioning reduces the cost of bringing a new drug to the market and increases the probability of success as the safety profile of the drug has been already studied for the initial indication (Ashburn & Thor, 2004). Moreover, new research fields in bioscience has enabled innovative companies to develop a health technology for various indications from the outset of research and development process (Medina-Franco, Giulianotti, Welmaker, & Houghten, 2013). Often the health benefits of a given technology vary substantially across indications. Garrison and Veenstra (2009), for example, showed that the health benefits of trastuzumab provided to late-stage breast cancer patients are three times larger than the ones provided to early-stage patients.

Health technologies provide differential health benefits even within a single indication. Nowadays, there are a larger number of treatments available for each clinical indication. As these treatments become more effective but more expensive, the financial cost of not prescribing the best therapy increases. A great deal of evidence shows that physicians may not prescribe the best treatment in the first instance. "Empirical therapy," in which physicians try various drugs to find the most effective one for a specific patient, is common for depressed patients. The trial-and-error process of each treatment may take several weeks with a risk of severe side effects and hospitalization (Berndt, Bhattacharjya, Mishol, Arcelus, & Lasky, 2002). Adverse drug reactions, which are sometimes caused by the wrong prescriptions, are blamed for 2 million hospitalizations and 100,000 death per year in the US alone (Shastry, 2006).

Innovative drug manufacturers may introduce a marker at the launch of a new health technology to distinguish between patient subgroups. Such markers may help physicians to identify the best treatment for a given patient. A marker is defined as a specific characteristic, or a set of characteristics, of a patient that determines the level of expected health benefit that the patient receives from a health technology. Patients might be divided into subgroups. A marker includes any diagnostic test or clinical observation that indicates a preferred treatment for a patient subgroup. A marker could be an easily observable characteristic (e.g., sex, age, or co-morbidities) or a latent characteristic that requires a specific test to measure (e.g., a specific gene mutation).

Markers have become more sophisticated over time. Many pharmaceutical companies, for example, have started to record the genetic profile of their clinical trials subjects (Ginsburg & McCarthy, 2001). Drugs that divide patients receiving similar health benefits into subgroups based on genetic variations across patients or across diseases have become more common. The US Food and Drug Administration, for example, recently published a list of a large number of drugs for which there is an identified genetic variant associated with a positive response.[33] Historically, stratification of patients had occurred after drug approval, when the variation in a medicine's clinical effects became better understood as a response to observable patient characteristics (Trusheim, Berndt, & Douglas, 2007). In many cases, the harmfulness of a drug was established only years after the drug was introduced to the market. For example, Plavix, an anti-blood clotting drug, was approved by FDA in 1997. In 2010, FDA added a boxed warning

[33] For further information, see http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm, accessed on November 10, 2015.

that this drug is not effective for patients that are CYP2C19 poor metabolizers, representing up to 14% of patients.[34]

During the research and development process, a manufacturer may strategically decide not to develop the drug for a given indication or not to introduce a potential marker. When a health technology has not been developed for an indication or the marker is not introduced, there are two possible explanations: either the clinical evidence was not satisfactory; or despite satisfactory clinical evidence, the economic incentive was inadequate. Previous literature has documented evidence of the strategic behaviour of manufacturers. Budish, Roin, and Williams (2015) show that the shorter time-to-market for late-stage cancer indications due to shorter life-expectancy of patients relative to early-stage indications has distorted the investment towards the former indications. They report that from 1973 to 2011, around 17,000 clinical trials were conducted for patients with recurrent cancer indications, 12,000 for late-stage indications, and only 6,000 for early-stage indications. The authors argue that fixed patent term distorts firms' incentives, leading them to invest in the indications with a short time to market. The evidence shows that the development processes of some health technologies have been terminated due to reimbursement concerns of manufacturers (Eichler *et al.*, 2010). In this chapter, I show that some pricing schemes may distort the incentive of innovative manufacturer in a similar way.

Previous research has analyzed the effect of VBP on the investment decisions of manufacturers, but it has overlooked strategic behaviour when there are various patient-types. Jena and Philipson (2008) argue that willingness-to-pay of the payer for each unit of health

[34] For further information, see http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm203888.htm , accessed on May 14, 2016.

benefit (e.g., measured in terms of QALY) determines how much social welfare is appropriated by producers, and that this sets the incentive for investment in health innovation. To the extent that such appropriation results in under- or over-investment in innovative health technologies, third-party payers can adjust it to control the stream of investments. In such models, the investment decision is considered as a one-time decision without any strategic component in it. In this model, I extend that literature by considering a manufacturer making decision during research and development process to target which indication and whether to distinguish different subgroups within an indication.

In designing value-based pricing schemes to deal with a health technology with multiple indications, the third-party payer can use different approaches. Claxton (2007) proposes that the price of multi-indication or multi-subgroup health technologies should be set at the margin, i.e. based on the health benefit of the lowest value, to enable the payer to receive a transfer from the manufacturers. Thornton (2007) proposes price discrimination with the justification that such pricing would incentivise incremental innovation. The implicit assumption in the proposed pricing schemes in this literature is that the division of patients into various indications and subgroups are exogenously determined and the health technology will be brought for all indications or subgroups at the same time. The key contribution of this chapter is that it incorporates the strategic decisions of the manufacturer with respect to indications and markers.

Another strand of the literature recognizes the entry of a health technology for different indication at different times. Garrison Jr and Veenstra (2009) and Lu *et al.* (2012) propose a pricing scheme in which the price adjusted upon entry of new indication and price is set based on the average value of all indications. In this chapter, I show that even though this pricing scheme does not distort the manufacturer's decision to seek approval, it does distort the prices of

incumbent and future technologies. Although considering the long-run effect of pricing schemes is not in the scope of this chapter, distorted prices distort the incentive of manufacturer in the same direction as explained for the new technology in this chapter.

The structure of the chapter is as follows. In the next section, I fully explain the structure of the game in which in the first period, a payer announces its pricing scheme. The manufacturer takes into account the chosen pricing scheme in its research and development decisions. Finally, patients and physicians decide which covered health technology to choose. In section 3, I explain the reaction of the manufacturers to chosen pricing schemes for the case of multi-indication and multi-subgroup case. The last part of this section describes the virtues and vices of each pricing scheme for the payer. Section 4 concludes the chapter.

4.2 Structure of the game

The structure of the games is the following. In the first stage, the third-party payer announces its pricing scheme for multi-type technologies. In the second stage, the manufacturer decides which patient-types to target and whether to identify the marker, if applicable. Finally, patients and physicians choose from an array of insured technologies. The solution is based on backward induction.

A third-party payer uses VBP to decide whether to include a new technology in its formulary (or list of approved drugs). As described below, the VBP scheme is straightforward when the new technology targets only one patient-type. For technologies beneficial to more than one patient-type, three VBP schemes are considered to investigate their effect on manufacturers' decisions to develop a technology and to seek marketing approval. The pricing schemes considered are the exhaustive list of those implemented and suggested in theoretical works.

Facing the VBP scheme, the manufacturer makes its development and marketing approval decisions. For simplicity, I assume a new technology offers benefits E_{jN} to two potential patient-types: one patient-type (high-type patients) receives higher health benefits from the new technology than the other (low-type patients) $E_{hN} > E_{lN}$. Each patient-type has a population of M_j where $M_h + M_l = M$. There exists an incumbent technology for each patient-type and the same order of health benefits may not apply to the incumbent technologies*:* $E_{hI} \gtrless E_{lI}$.

The division of patients into types can take two forms. First, this division can be determined *exogenously* by regulatory agencies or other parties. In this case, the manufacturer knows at the outset that it needs to get marketing approval for each patient-type separately. I label this the multi-indication case. Indications could be part of a broad disease area, such as early-stage or late-stage cancer, or two indications for unrelated disease areas such as cancer and macular degeneration. Second, the division of patients could be determined *endogenously* through research and development; the information generated by the manufacturer may provide insights that some patients are different from others. The process of dividing patients into subgroups requires validating a reliable marker or test. I call this the multi-subgroup case. The manufacturer has proprietary right on the information generated throughout its clinical trials. Thus, targeting which patient-types and validating the marker depends on the manufacturer's decisions to generate the relevant information. After the product is approved for specific indications or subgroups, patients and physicians decide which technology to utilize.

4.2.1 The payer

Cost-effectiveness based (CE-based) policies have long guided the allocation of resources among various stakeholders, from third-party payers to hospitals. The incremental cost-effectiveness

ratio (ICER) is the backbone of conventional CE-based policies, representing the cost per unit of health benefits measure (e.g., quality-adjusted life-years) that a particular health intervention provides to patients. Deciding whether to adopt the new intervention, the payer needs to compare a new health intervention's ICER to its willingness to pay for each unit of health benefit:

$$\frac{c_{aN} - c_{aI}}{E_{aN} - E_{aI}} \leq \lambda \tag{4.1}$$

where λ represents the insurer's willingness to pay for each unit of health benefit, and c_{aN} and c_{aI} are the average cost of new and incumbent interventions across all targeted patients to the payer. If equation (4.1) is satisfied, the new technology is deemed cost-effective and will be adopted (Johannesson & Weinstein, 1993).

Conventional CE-based policies provide a straightforward rule for adopting new health technologies that provide health benefits to different patients. The health intervention is adopted only for patient-types with an ICER smaller than the payer threshold. Such inclusion rules have been implemented by issuing guidelines that determine what patient-types are eligible to receive specific health interventions (Coyle, Buxton, & O'Brien, 2003).

Conventional CE-based policies do not provide any clear way of dealing with a large fixed cost (Garber, 2000). Pharmaceutical products and medical devices involve substantial upfront research and development investments. For these products, typically the marginal cost of production is a small fraction of the price when these health technologies are under patent protection. Given the existence of a large fixed cost, the mechanical adoption criterion of the payer is transformed to a decision made by manufacturers. In effect, the role of third-party payers as the adoption decision-makers means that they are implicit price-setters. The term

"value-based pricing"[35] emerged as CE-based policies evolved from an adoption policy rule to a framework for designing pricing schemes. In VBP system, the upper bound of the payer's acceptable price for a new technology is derived from Equation (4.1):

$$p_{aN} \leq v_{aN} + (p_{aI} - v_{aI}) \tag{4.2}$$

where v_{aN} and v_{aI} are the average monetary values of the new and incumbent treatments. The value is simply calculated as the product of the willingness to pay of the payer (λ) and the average health benefit of the technology (E). In such a pricing scheme, the price of the new technology hinges on its absolute value to patients and also how the alternative treatment is priced. If the incumbent technology is value-based priced, then $p_{aI} - v_{aI}$ is zero, and the new technology's absolute value is the only determinant of its price.[36] In this chapter, I focus on the case where the existing technologies are value-based priced.

Value-based pricing schemes determine the upper limit of the acceptable price for a new health technology. Given common knowledge about the pricing schemes, the manufacturer responds to them by setting price equal to the highest price acceptable to the payer (Jena & Philipson, 2013). This implies that the price equals the value of the targeted patient-type:

$$p_{aN} = v_{aN} \tag{4.3}$$

The price of the health technology is the same across all the schemes I consider when only one patient-type *i* is targeted:

$$p_{iN} = v_{iN} \tag{4.4}$$

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[35] The Value-based pricing term was coined by UK Office of Fair Trading in 2007 when UK contemplating whether to use such CE-based policies in pharmaceutical market.

[36] If the alternative treatment is priced based on cost, e.g., price for off-patent technologies, then $p_{aI} - v_{aI} \leq 0$, and therefore the manufacturer receives a smaller price than its technology's absolute value.

The situation gets more complicated for technologies with multiple indications or subgroups. The suggested and implemented pricing schemes revolve around two general pricing schemes: uniform pricing and price discrimination. Uniform pricing can be categorized into two types of value-based pricing schemes depending on how the single price is set. In the marginal value-based pricing (MVBP) scheme, the price is set at the value of the marginal patient-type, the one receiving the lowest value (Claxton, 2007):

$$p_{aN} = v_{lN} \tag{4.5}$$

MVBP has been implemented in some countries, including, for example, Sweden (Persson, Willis, & Odegaard, 2010).

Garrison and Veenstra (2009) and Lu *et al.* (2012) suggest another single-price scheme according to which the price is adjusted based on the value of new indications or patient-types. I call this pricing scheme average value-based pricing (AVBP). The basis for the price is the weighted average value across all patient-types:

$$p_{aN} = \phi_h v_{hN} + \phi_l v_{lN} \tag{4.6}$$

where $\phi_j = \frac{M_j}{M}$ denotes the share of j type patients in the total targeted population. AVBP has been implemented in several countries such as France, Italy, Belgium, and Australia (Paris & Belloni, 2013).

Price discrimination, which is called differential value-based pricing (DVBP) scheme in this chapter, allows the manufacturer to discriminate across patient-types:

$$p_{iN} = v_{iN} \; where \; i = l, h \tag{4.7}$$

In this case, the price is set based on each indication's value and reimbursing one indication does not affect the price for the other. This pricing scheme has been used for some

specific drugs, but not as a general rule. For example, Italy has reimbursed sunitinib for two cancer indications at two different prices in a scheme similar to DVBP (Paris & Belloni, 2013).

I assume that the payer has full information about patients' expected health benefits, but cannot distinguish patients based on their health benefits. Put another way, the payer cannot validate the marker if it is not validated by the manufacturer. The payer also provides full coverage for adopted health technologies.

4.2.2 The manufacturer

First, the manufacturer needs to ensure that its new technology reaches patients. To this end, the manufacturer needs to get marketing approval from each jurisdiction's regulatory agency (e.g., the Food and Drug Administration in the USA). Then the manufacturer needs to get its new technology listed in the payer's formulary. In this chapter, I assume the production of new health technologies only involves the upfront R&D costs, and the marginal production cost is zero. The production cost of pharmaceutical products and medical devices, in fact, is a small fraction of the price when they are under patent. This fact is evident when the price after patent expiration of these health technologies are compared with the price when they are under patent. The result when production cost is included in the model does not differ qualitatively with that of when they are not considered.

The development process of health technologies proceeds in a sequential order.[37] Following basic research and animal trials, the innovative manufacturer starts generating evidence required by the regulatory agencies and the payers. Generating evidence about the safety and efficacy of a new health technology occurs through three phases of clinical trials.

[37] For an extensive explanation of this process take a look at Malani & Philipson (2012) and DiMasi *et al.* (1991).

Each phase is designed to generate a specific type of information. In phase I, a small number of usually healthy volunteers are involved to gather information on metabolism, excretion, toxicity, and acute side effects of the technology and also safe dosing ranges. Phases II and III are conducted on people with the targeted medical condition. Phase II trials are medium-size studies that provide early evidence that the new technology is safe and efficacious. In phase III trials, the technology is studied in a larger group of volunteers to firmly establish safety and efficacy of the new technology and to uncover any less frequent side effects.

For technologies beneficial to multi-type patients, the development process for each patient-type shares basic research, animal trials, and some phases of clinical trials. Basic research, animal trials, and Phase I studies are usually not related to a specific patient-type and developing the health technology for all patient-types can rely on the result of early parts of research and development (Ashburn & Thor, 2004). Thus, all patient-types share the early parts of research and development. On the other hand, phase II and phase III studies are specific to each patient-type, and thus, must be conducted for each indication or patient-type. When the division of patients is exogenous, the shared fixed costs incorporate costs of the early parts of research and development. However, when the division of patient-types is endogenous, the manufacturer needs to incur an additional cost: the cost of detecting and validating the potential marker that distinguishes patients from each other. The detection studies are usually followed in parallel with the early phases of clinical trials. The validation process requires a suitable design of the later phases of clinical trials, which involve a larger number of human subjects. To consider these features of research and development process, I assume that fixed cost has three components: two fixed costs that are specific to each patient-type (C_{hN} and C_{lN}) and a shared fixed cost that is not specific to patient-types (C_{sN}). In the case of multi-indication technologies,

this shared fixed cost contains only the cost of early parts of research and development ($C_{sN} = C_{dN}$). For the multi-subgroup case, however, the shared fixed costs have two components: the cost of validating the marker C_{mN} and early parts of research and development C_{dN} (i.e., for the multi-subgroup case $C_{sN} = C_{dN} + C_{mN}$).

To obtain marketing approval, manufacturers are required to provide evidence that the benefit of the new technology outweighs its risk relative to placebo. Thus, the health benefit of a new technology is assessed based on its own merits, and providing comparative evidence relative to other existing treatments is not usually required. Regulatory agencies consider a health technology safe and efficacious when patients on average receive positive health benefits:

$$E_{iN} > 0 \tag{4.8}$$

After obtaining regulatory approval, the manufacturer needs to get its health technology listed in the third-party payer's covered technologies. The evidence requirement of insurers using value-based pricing schemes usually differs from that of regulators. The insurer in principle assesses the incremental value of the new technology to patients relative to existing treatments in the real world setting (incremental effectiveness), instead of considering its absolute benefits in an ideal environment (absolute efficacy) (Eichler *et al.*, 2010). Such evidence may be developed alongside clinical trials by using existing technologies as active comparators and using standardized health benefit measures (Hughes, 2008), e.g. quality-adjusted life-years, or conducting new studies after filing approval application. However, evidence generated before market approval, especially phase III, is typically used for almost all coverage and payment decisions (Persson *et al.*, 2010).

The second consideration of the manufacturer is to make sure that it receives positive total revenue after seeking approval for the health technology. This will only be the case if the

new health technology is better than the incumbent. Given that patients only consider health technologies' effectiveness in choosing which one to utilize, a new technology with lesser effectiveness than that of the incumbent will not result in positive sales.

The last consideration for the manufacturer is whether the new technology generates positive profits for each patient-type. To make the model tractable, I define the quasi-rent (π) of each patient-type as the difference between its revenue and its specific fixed cost:

$$\pi^{iT} = M_i v_{iN} - C_{iN} \quad for\ i = l, h \tag{4.9}$$

The profit of targeting only one patient-type is the difference between its specific quasi-rent and any other shared fixed costs. This profit does not depend on the pricing schemes:

$$\Pi^{iT} = \pi^{iT} - C_{sN} \quad for\ i = l, h \tag{4.10}$$

The profitability of advancing the new technology for both patient-types depends on the pricing scheme. Under DVBP the price for one indication is independent of the other, so the profit, in this case, will be:

$$\Pi^{bT}_{DVBP} = \pi^{hT} + \pi^{lT} - C_{sN} \tag{4.11}$$

Under AVBP, the price for both indications is the same and equals the average price of patient-types (equation (4.6)). Therefore, its revenue is the same as the DVBP, and so is the profit for targeting both patient-types. However, under MVBP, the price for both indications is the same and equals the value for the low-type patients. The profit of targeting both patient-types under MVBP can therefore be written as:

$$\Pi^{bt}_{MVBP} = \pi^{hT} + \pi^{lT} - C_{sN} - T \tag{4.12}$$

where the last term is the "transfer" that the payer captures by setting MVBP as the pricing scheme:

$$T=M_h(v_{hN}-v_{lN}) \quad (4.13)$$

The development of new health technologies is implemented sequentially. At several points, the manufacturer decides whether to proceed with the development process. In this chapter, I assume that at the outset of research and development, the manufacturer has full information about the health benefits provided by the new technology for each patient-type, the existence of the potential marker, and the fixed costs of development. Taking into account the informational requirement of the regulatory agencies and the pricing scheme of the payer, the manufacturer makes an investment decision that maximizes its profit.

4.2.3 Patients and physicians

Patients are diagnosed by physicians, and if necessary, patients and physicians together consider treatment options. Patients are fully covered, and thus, the price is not a factor in their decision. Based only on available information about effectiveness, they choose one technology from an array of covered technologies. This assumption implies that patients and physicians choose the health technology based on evidence regarding health benefits only. Azoulay (2002) has shown that scientific evidence regarding the safety and efficacy of pharmaceutical products in anti-ulcer therapeutic area has a profound effect on their diffusion. Each patient utilizes one unit of a health intervention and receives some health benefits from it. The role of patients and physicians is trivial in this model and is not considered in the rest of the chapter.

4.3 Solution of the game

4.3.1 The manufacturer

In this section, I analyze the pre-launch behaviour of a manufacturer whose new health technology potentially benefits different groups of patients. I first consider the case in which the targeted population is divided exogenously and distinguished by currently defined criteria, e.g.,

indication, so that the manufacturer needs to conduct clinical trials for each indication. I then proceed to analyze the case in which the manufacturer may validate the potential marker that can distinguish patient-types, e.g., subgroups, who receive differential health benefits.

Information about costs and the result of clinical trials are the manufacturer's proprietary information. Other parties can access the information only if the manufacturer decides to make the information public. The proprietary right of information implies that if the manufacturer seeks approval for only one patient-type, the reason is not apparent to other parties: for example, the reason may be that the potential health benefits for the other patient-type was not satisfactory, or that the potential revenue was not acceptable, or that the profit was negative, or that the manufacturer was behaving strategically. The same applies to the marker-validation decision of the manufacturer.

4.3.1.1 Development decision in multi-indication case

Given the exogenous division of patients in the multi-indication case, the marketing approval process guarantees that both patient-types on average receive positive health benefits from the new technology ($E_{iN} > 0, i = h, l$). To explore the effect of pricing schemes on the behaviour of the manufacturer, I assume the incumbent technologies are brought to the market by two different manufacturers. There is no restriction on the relationship between the health benefits of the new and incumbent technologies for either indication ($E_{iN} \lesseqgtr E_{iI}$).

In terms of revenue, the manufacturer faces various scenarios. Given the assumption that patients choose the technology with the highest health benefits, the manufacturer earns positive revenue if the new technology's values for both indications are greater than those of the incumbent treatments. Otherwise, the patients would keep utilizing the incumbent treatments. However, if the evidence shows that the new technology provides smaller health benefits for one

or both indications, the manufacturer would receive zero revenues from that or those indications. The only viable option for the manufacturer, in this case, is to develop the health technology for one or none of the indications. The outcome for those scenarios does not differ across pricing schemes and won't be discussed in this section.

When the new technology provides higher health benefits for both indications, the manufacturer has three choices over which indications it will seek approval: only high-type patients (*hT*), only low-type patients (*lT*), or alternatively both types (*bT*). The diagram below portrays the game in this case.

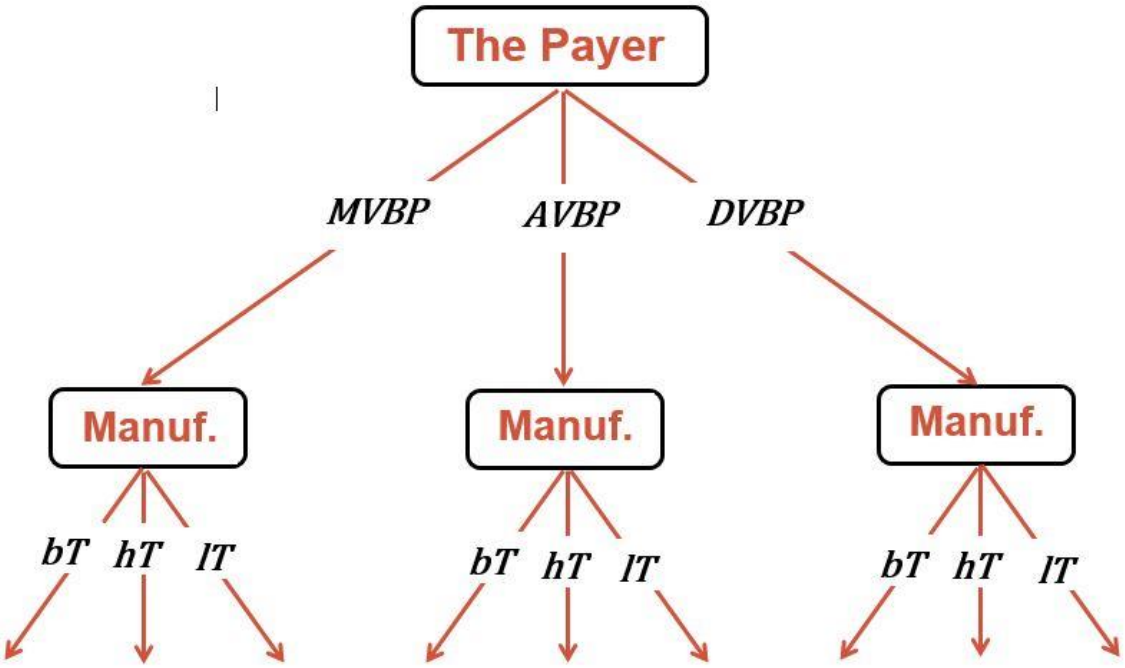

Figure 4.01: Illustration of the game in the multi-indication case

Proposition 4.1: Assume $v_{iN} > v_{iI}$ for $i = h, l$. Then, under DVBP and AVBP, the manufacturer seeks approval for:

a) both indications if and only if:

$$\pi^{hT} + \pi^{lT} - C_{dN} > 0 \quad (4.14)$$

$$\pi^{hT} > 0 \quad (4.15)$$

$$\pi^{lT} > 0 \quad (4.16)$$

b) only high-type indication if and only if:

$$\pi^{hT} - C_{dN} > 0 \quad (4.17)$$

$$\pi^{lT} < 0 \quad (4.18)$$

c) only low-type indication if and only if:

$$\pi^{lT} - C_{dN} > 0 \quad (4.19)$$

$$\pi^{hT} < 0 \quad (4.20)$$

d) no indication otherwise.

The manufacturer will enter both markets if the sum of quasi-rents is greater than the shared fixed cost (i.e., equation (4.14) satisfies). This equation also implies that both indications contribute to recovering the shared fixed cost. The magnitudes of quasi-rents (π^{hT} and π^{lT}) determine how much each indication contributes in recovering the shared fixed cost. In this situation, as long as the quasi-rent of an indication is positive (i.e., equation (4.15) and (4.16) are satisfied), the manufacturer would seek approval for both regardless of how much each contributes to the recovery of shared fixed cost.

If the quasi-rent of one indication decreases to a negative number (equations (4.18) or (4.20) are satisfied), then there is no incentive for the manufacturer to develop and seek approval for that indication. In such a case, the manufacturer would develop the technology for the other indication only if its quasi-rent is big enough to recover the cost of early-stage and late-stage development process (equations (4.17) or (4.19) are satisfied).

Proposition 4.2: Assume $v_{iN} > v_{iI}$ for $i = h, l$. Then, under MVBP, the manufacturer seeks approval for:

a) both indications if and only if:

$$\pi^{hT} + \pi^{lT} - C_{dN} - T > 0 \quad (4.21)$$

$$\pi^{hT} > T \quad (4.22)$$

$$\pi^{lT} > T \quad (4.23)$$

b) only high-type indication if and only if:

$$\pi^{hT} - C_{dN} > 0 \quad (4.24)$$

$$\pi^{lT} < T \quad (4.25)$$

$$\pi^{hT} > \pi^{lT} \quad (4.26)$$

c) only low-type indication if and only if:

$$\pi^{lT} - C_{dN} > 0 \quad (4.27)$$

$$\pi^{hT} < T \quad (4.28)$$

$$\pi^{hT} > \pi^{lT} \quad (4.29)$$

d) no indication otherwise.

As discussed above, under MVBP, a uniform price is set for both types, which equals the value provided to low-type patients. This pricing scheme reduces the manufacturer's quasi-rent from the high-type patients relative to other pricing schemes. The magnitude of reduction in the quasi-rent equals the amount of transfer that the payer receives (Equation (4.12)).

The manufacturer takes the transfer into account in its development strategy. The transfer can be seen as an extra cost of seeking approval for both patient-types, and thus, increases the threshold for the sum of quasi-rents that make the *bT* strategy profitable; the sum of quasi-rents

should increase to the point that recovers the sum of the shared fixed cost and transfer (equation (4.21) is satisfied). Moreover, the quasi-rent for each indication must be greater than the magnitude of transfer (equations (4.22) and (4.23) are satisfied) for the manufacturer to choose to develop the technology for both indications.

If the quasi-rent of one indication is smaller than the amount of transfer (equation (4.25) or (4.28) is satisfied), the manufacturer may move to the single indication strategy. The magnitude of transfer (T) and shared fixed costs (C_{sN}) plays a role in determining which single-indication strategy is chosen by the manufacturer. In the case where $T < C_{sN}$, the indication with smaller quasi-rent than the transfer is not a viable option for single-type strategy as its quasi-rent is not large enough to recover the shared fixed cost. In this case, equations (4.26) and (4.29) are not binding. If the quasi-rent of the other indication is large enough to recover shared fixed cost (equation (4.24) or *(4.27)* is satisfied), the manufacturer would seek approval for it. When $T > C_{sN}$, however, the indication with smaller quasi-rent than transfer may still recover the shared fixed costs, and still remains as a viable option for the single-type strategy. In such a case, manufacturer compares the quasi-rents to seek approval for the indication that generates larger quasi-rent, and equations (4.24) and (4.27) are not binding anymore.

4.3.1.2 Development decision in multi-subgroup case

I have characterized the outcomes of the model when the division of patient-types is exogenously determined. I now consider the case with endogenous division of patient-types. The health benefits received by patients within a single indication often depend on some potentially observable characteristic of the patient or the disease, so that it is in principle possible to identify subgroups of patients who will receive, on average, heterogeneous benefits. Dividing patients into subgroups requires that the manufacturer detect and validate a "marker". Finding a

characteristic or a set of characteristics (the so-called marker) that predicts the responsiveness and the level of effectiveness of a technology is inherently complex and costly. The manufacturer selects several characteristics out of the millions of genetic and non-genetic traits of patients and diseases during research and development. This process happens before phase II clinical trials, enabling the manufacturers to test them on phase II and phase III participants (Davis, Furstenthal, & Desai, 2009). For example, in oncology, the most explored therapeutic area for markers, from more than 50 potentially useful markers only a handful are generally valid (McKinsey, 2013). Thus, even after phase I trials, the manufacturer has imperfect knowledge about the validity of markers. In addition, the marker validation process normally requires recruiting a large number of patients in phase II and phase III clinical trials, to enable the manufacturer to identify responder and non-responder patient groups during clinical trials.

The manufacturer first needs to obtain regulatory approval. This process does not usually require the comparison of the new technology with the existing ones. It is possible that even though some patients would not receive any health benefits, the product could be approved. For example, for some medical conditions such as rheumatoid arthritis, more than 50 percent of patients do not respond to the approved treatments (McKinsey, 2013). In the notation of my model, this can be shown by considering that regulatory approval is based on the effectiveness of the treatment in the whole patient population:

$$E_{aN} > 0. \tag{4.30}$$

Given the assumption of the model that the received health benefits are larger for high-type patients than for low-type patients, low-type patients may receive negative health benefits. The lower bound for low-type patients that the marketing approval requirement for the whole

population is still satisfied is $E_{lN} = -\frac{M_h}{M_l} E_{hN}$. However, if the marker is validated, the manufacturer cannot pass the regulatory approval for a health technology with negative health benefits for an identified subgroup. This implies that the health benefits provided to low-type patients must be positive if the marker is validated.

The second consideration of the manufacturer is to make sure it receives positive revenue. For this purpose, the manufacturer needs to show that its technology provides greater health benefits than the incumbent technologies. When no marker is identified, this boils down to comparing the average health benefits across subgroups. However, when the marker is identified, patients observe the relative effectiveness of the new and incumbent technologies for each subgroup separately.

Thus, the manufacturer can use marker identification strategically, only validating the marker when it is likely to be useful. Sun and her coauthors (2011) provide evidence of such strategic behaviour. Analyzing a sample of published randomized clinical trials, they illustrate that when the health outcome of technologies for the whole population is not satisfactory, the industry funded randomised clinical trials are 2.3 times more likely to conduct and report subgroup analysis. This tendency to report subgroup analysis is absent when the health outcome for the whole population is satisfactory.

The game in this section differs from the multi-indication case as the manufacturer makes decisions about both marker validation and seeking approval. At the first decision node, the manufacturer decides whether to validate the potential marker. If the manufacturer decides not to validate the marker, the only viable strategy is seeking approval for the whole population. I call this the "no marker" (*NM*) strategy. Given this strategy, all patients will be covered at a price

reflecting new technology's average value as there is no information about the existence of subgroups. When the manufacturer decides to validate the marker, however, the set of strategies in front of the manufacturer is identical to those of multi-indication case. However, the profit differs in this case as the shared fixed cost in the multi-subgroup case is the sum of costs of the early parts of research and development and the costs of validating marker ($C_{sN} = C_{dN} + C_{mN}$).

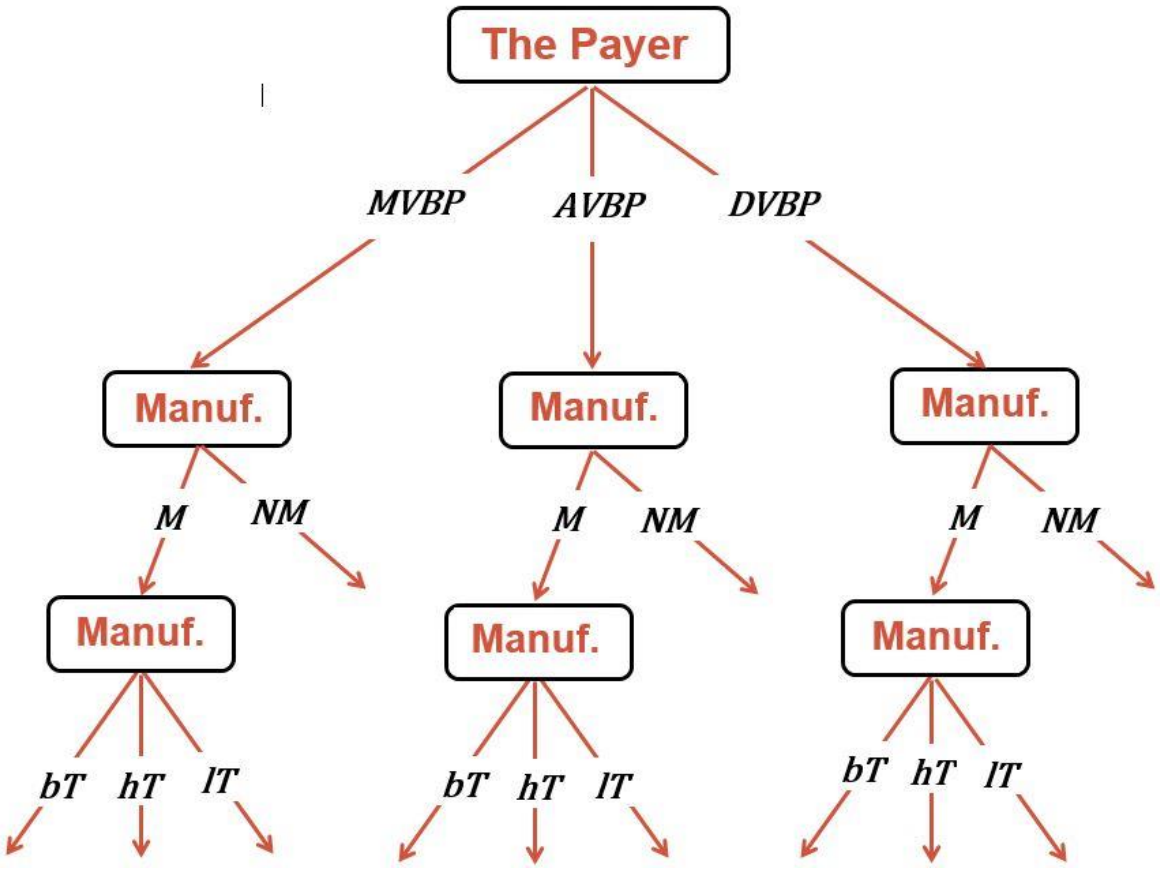

Figure 4.2: Illustration of the game in the multi-subgroup case

Proposition 4.3: Assume $v_{iN} > v_{iI}$ for $i = h, l$. Then, the manufacturer seeks approval for:

a) the whole population without validating the marker if and only if:

$$\pi^{hT} + \pi^{lT} - C_{dN} > 0 \qquad (4.31)$$

$$\pi^{hT} > -C_{mN} \qquad (4.32)$$

$$\pi^{lT} > -C_{mN} \quad (4.33)$$

b) the high-type subgroup if and only if:

$$\pi^{hT} - C_{dN} - C_{mN} > 0 \quad (4.34)$$

$$\pi^{lT} < -C_{mN} \quad (4.35)$$

c) low-type subgroup if and only if:

$$\pi^{lT} - C_{dN} - C_{mN} > 0 \quad (4.36)$$

$$\pi^{hT} < -C_{mN} \quad (4.37)$$

d) no subgroup otherwise.

Given $v_{iN} > v_{il}\ for\ i = h, l$, the new technology provides a positive health benefit to both subgroups, implying that regulatory and reimbursement approval are both guaranteed. The introduction of *NM* strategy to the model, however, dominates the *bT* strategy. The manufacturer can target both subgroups through following *bT* and *NM* strategies, though the former requires investing in marker validation, and increases the cost of bringing the new technology to the whole population. So long as both marketing approval and getting positive revenue are guaranteed, which they are in this case, the manufacturer does not have any incentive to invest in marker validation to target the whole population.

The threshold for moving from targeting both patient-types to one decreases relative to the multi-indication case. As we saw in the previous section, when the quasi-rent of providing the new technology to one patient-type turns negative, the manufacturer does not target that patient-type. Having the *NM* strategy option, the manufacturer only moves to single-subgroup strategy if the quasi-rent is negative, and its absolute magnitude is larger than the cost of validating the marker (i.e., equation (4.35) or (4.37) are satisfied).

Comparing this result with the multi-indication case, *Proposition 4.3* indicates that as long as seeking approval with no marker is profitable for the manufacturer of the new technology, the manufacturer would not validate the potential marker. This results since the manufacturer cannot appropriate the benefit of identifying subgroups.

Proposition 4.4: Assume $v_{hN} > v_{hI}$ *and* $v_{lN} < v_{lI}$.

a) if:

$$v_{aN} > v_{aI} \tag{4.38}$$

then, the manufacturer seeks approval for:

a1) the whole population without validating the marker if and only if:

$$\pi^{hT} + \pi^{lT} - C_{dN} > 0 \tag{4.39}$$

$$\pi^{lT} > -C_{mN} \tag{4.40}$$

a2) high-type subgroup if and only if:

$$\pi^{hT} - C_{dN} - C_{mN} > 0 \tag{4.41}$$

$$\pi^{lT} < -C_{mN} \tag{4.42}$$

b) if:

$$v_{aN} < v_{aI} \tag{4.43}$$

the manufacturer would seek approval for high-type subgroup if and only if:

$$\pi^{hT} - C_{dN} - C_{mN} > 0 \tag{4.44}$$

c) the manufacturer would seek approval for no subgroup otherwise.

Proposition 4.5: Assume $v_{hN} < v_{hI}$ *and* $v_{lN} > v_{lI}$.

a) If:

$$v_{aN} > v_{aI} \tag{4.45}$$

Then, the manufacturer seeks approval for:

a1) whole population without validating the marker if and only if:

$$\pi^{hT} + \pi^{lT} - C_{dN} > 0 \quad (4.46)$$

$$\pi^{hT} > -C_{mN} \quad (4.47)$$

a2) high-type subgroup if and only if:

$$\pi^{lT} - C_{dN} - C_{mN} > 0 \quad (4.48)$$

$$\pi^{hT} < -C_{mN} \quad (4.49)$$

b) if:

$$v_{aN} < v_{aI} \quad (4.50)$$

the manufacturer would seek approval for high-type subgroup if and only if:

$$\pi^{lT} - C_{dN} - C_{mN} > 0 \quad (4.51)$$

c) The manufacturer would seek approval for no subgroup otherwise.

Proposition 4.4 and *Proposition 4.5* are similar with one difference: in the former the value of low-type patients is smaller than that for the incumbent while in the latter the value of high-type patients is smaller than that for the incumbent. Therefore, I just explain the *Proposition 4.4*.
In this case, the manufacturer would pass the regulatory approval even though the health benefits provided by the new technology to one patient-type are lower than that provided by the incumbent technology. Two situations are conceivable; the average health benefit of the new technology is greater or lower than that of the incumbent.

I begin with the case where the value of the new technology is on average larger than the value of the incumbent (i.e., (4.38) holds). In this case, the manufacturer can bring the new technology to the market and attract the whole population after getting coverage from the payer if this strategy is profitable (i.e., (4.39) holds). If the quasi-rent of low-type patients is negative

and its absolute magnitude is larger than the marker validation cost (i.e., (4.42) holds), then the manufacturer may move to targeting only high-type subgroup. This happens if the quasi-rent of the high-type patients is large enough to recover the shared fixed costs (i.e., (4.41) is satisfied).

The same thing would not happen when the quasi-rent of the high-type patients is negative. The manufacturer knows that targeting only low-type patients means zero sales, and the only way to generate positive revenue is to target the whole population. As long as the positive quasi-rent of low-type patients compensates for the negative quasi-rent of the high-type patients to the extent that keeps profit positive (i.e., (4.39) holds), there is no lower bound for the negative quasi-rent of the high-type subgroup.

In the case where the average value of the new technology for the whole population is lower than that for the incumbent technology (i.e., (4.43) holds), the manufacturer would target the high-type subgroup if its quasi-rent is large enough to recover the shared fixed cost.

In this situation, the manufacturer cannot receive any revenue from low-type patients if the marker is validated. So long as bringing the technology for the whole population without validating the marker is possible and profitable, it will do that to maximize its profit. Note that when the technology is on the market, manufacturers have little incentive to determine which subgroup of patients gain the most from the drug as manufacturers may lose sales from other subgroups (Scott Morton & Kyle, 2011). This strategic behaviour of the manufacturer deprives the low-type patients of the better health technology.

Proposition 4.6: Assume $v_{hN} > v_{hI}$ and $v_{lN} < 0$.

a) if:

$$v_{aN} > v_{aI} \qquad (4.52)$$

then, the manufacturer seeks approval for:

a1) the whole population without validating the marker if and only if:

$$\pi^{hT} + \pi^{lT} - C_{dN} > 0 \quad (4.53)$$

$$\pi^{lT} > -C_{mN} \quad (4.54)$$

a2) high-type subgroup if and only if:

$$\pi^{hT} - C_{dN} - C_{mN} > 0 \quad (4.55)$$

$$\pi^{lT} < -C_{mN} \quad (4.56)$$

b) if:

$$v_{aN} < v_{aI} \quad (4.57)$$

the manufacturer would seek approval for high-type subgroup if and only if:

$$\pi^{hT} - C_{dN} - C_{mN} > 0 \quad (4.58)$$

c) The manufacturer would seek approval for no subgroup otherwise.

Given $v_{hN} > v_{hI}$ and $v_{lN} < 0$, the value of the new technology for the low-type patients is negative. As a result, if the marker is identified, the new technology cannot clear the marketing approval requirement for this patient-type. Note that the quasi-profit for this patient-type is negative and the manufacturer is willing to validate the marker if it is costless. If validating the marker is costly, the manufacturer compares the negative quasi-rent of the low-type patients and the marker validation cost. If the absolute magnitude of the former is smaller than the latter (i.e., equation *(4.54)* is satisfied), the manufacturer will not identify the maker and will target the whole population, even though some patients will be harmed. This occurs as long as the sum of quasi-rents is greater than the shared fixed cost (i.e., equation (4.53) satisfies).

When the average value of the new technology is smaller than that for the incumbent (i.e., equation (4.57) is satisfied), the manufacturer will seek approval for the high-type patients if it provides positive profit (i.e., equation (4.58) is satisfied).

Proposition 4.7: Assume $v_{hN} < v_{hI}$ and $0 > v_{lN} > v_{lI}$. The manufacturer would seek approval for

a) the whole population without validating the marker if and only if:

$$v_{aN} > v_{aI} \tag{4.59}$$

$$\pi^{hT} + \pi^{lT} - C_{dN} > 0 \tag{4.60}$$

b) no subgroup otherwise.

Given $v_{hN} < v_{hI}$ and $0 > v_{lN} > v_{lI}$, even though the value of the new technology for the low-type patients is negative, but because it is greater than that of the incumbent, the average value of the new technology may only be greater than that of the incumbent if the manufacturer does not identify the patient-types. In this case, if the quasi-rent of the high-type patients is large enough to compensate for the negative quasi-rent of low-type patients and the shared fixed cost, then the manufacturer would seek approval for the whole population without validating the marker. Note that if the average value of the new technology is smaller than that of the incumbent, the manufacturer would not be able to clear the marketing and reimbursement approval.

4.3.2 The payer

In this section, I discuss the implications of the manufacturers' behaviour facing the pricing schemes and information requirements for the payer. I first consider the distortion in the price of currently available technologies and also future technologies that each pricing scheme may generate. This effect is common across multi-indication and multi-subgroup cases. Second I examine the virtues and vices of each pricing scheme for the payer. The pricing schemes do not have any effect on the behaviour of manufacturers in the multi-subgroup case, but just multi-indication case. Finally, I consider the information requirement of the regulatory agencies and the payers. This part is related to the multi-subgroup case.

4.3.2.1 Distortion in prices

The model in the previous section addressed the decisions of the manufacturer of a new technology under different pricing schemes. After its launch, the new technology becomes the benchmark against which incumbent treatments are re-evaluated.[38] Therefore, the price of incumbent technologies should be adjusted after the new technology is listed in the formulary list of the payer. With a dynamic perspective, the effect on the price of future entrants also should be taken into account, even though it is not in the scope of the model in this chapter. If the new technology has distorted prices, it can also affect the prices of the future technologies. The analysis below is related to the multi-indication model. In the multi-subgroup model, the occurrence of price distortion is affected by whether the manufacturer validates the marker or not. If the manufacturer does not validate the marker the base price for future entrant resembles the AVBP scheme.

Proposition 4.8: When the manufacturer seeks approval for both indications, MVBP and AVBP creates a price distortion for incumbent technologies. DVBP does not create any price distortion.

Under MVBP and AVBP, the prices of both indications are set at the same level whenever the manufacturer brings the new technology for both. Such a setting creates a discrepancy between price and value for one or both patient-types. To illustrate Proposition 4.8, I start with the distortion resulting from MVBP and then I explain distortion created by AVBP.

[38] In UK, emergence of new evidence, a new entrant, and also a patent expiry leads to price adjustments for all drugs in a therapeutic area (Towse, 2007).

Suppose that under MVBP, the manufacturer decides to bring the new technology for both indications. Re-organizing equation (4.2) to reflect the impact of the pricing of the new technology on the incumbent technologies, we obtain:

$$p_{iI} = v_{iI} + (p_{iN} - v_{iN}) \tag{4.61}$$

Equation (4.61) differs from equation (4.2) in taking the new technology as the benchmark for determining the price of an incumbent technology for patient-type i.

Under MVBP the price of the new technology for both patient-types is equal: $p_{hN} = p_{lN} = v_{lN}$. This makes the price equal to average value of low-type patients. The incumbent technology for the high-type indication is re-evaluated based on the new technology whose price is lower than the value it provides:

$$p_{hN} - v_{hN} = -(v_{hN} - v_{lN}) < 0 \tag{4.62}$$

Therefore, the price for the incumbent technology serving the high-type patients will be:

$$p_{hI} = v_{hI} - (v_{hN} - v_{lN}) \tag{4.63}$$

indicating the price for the incumbent technology should be adjusted downward.

Under AVBP scheme, prices for both indications are different from the value of the new technology; the price for high-type patients is below its value while the price for low-type patients is greater than its value:

$$v_{lN} < p_N = (\phi v_{hN} + (1 - \phi) v_{lN}) < v_{hN} \tag{4.64}$$

The discrepancy in value and price for high-type patients resembles the distortion under MVBP for high-type patients, though with a different magnitude:

$$p_{aN} - v_{hN} = -(1 - \phi)(v_{hN} - v_{lN}) < 0 \tag{4.65}$$

However, the discrepancy in value and price for low-type patients is positive which leads to a price premium for incumbent technology serving the low-type market:

$$p_{aN} - v_{lN} = \phi(v_{hN} - v_{lN}) > 0 \quad (4.66)$$

DVBP does not distort the prices in any way as it treats each market independently.

The distortion in the price of multi-type technologies carries through to future technologies. This is potentially important in shifting incentives for investment into future technologies. The distortion in the price of future products could of course lead to distortion in approval seeking of manufacturers as discussed in section 4.2.

Note that these price adjustments are not related to any event in the market for one indication. This is the effect of pricing schemes which relate the price for one market to another.

4.3.2.2 Which pricing scheme?

To see the effect of each pricing scheme, I compare the reaction of the manufacturer to different pricing schemes. Moving to an MVBP from other pricing schemes would change the strategy of the manufacturer from seeking approval for both indications to a single-indication or none at all in some circumstances. The move from seeking approval for both types under DVBP and AVBP to one indication under MVBP occurs when the quasi-rent of one indication falls in the range of $0 < \pi^{iT} < T$ and the quasi-rent for the other indication is $\pi^{jT} > C_{dN}$.[39] In other words, this case resembles a situation where the quasi-rent of one indication makes up a large share of the cost recovery, and the other one makes a small contribution to the recovery of the shared fixed costs. Recall that quasi-rents of an indication is the revenue minus specific cost of that indication:

$$\pi^{iT} = M_i v_{iN} - C_{iN} \quad for\ i = l, h \quad (4.67)$$

[39] This section is explained for the case where $T > C_{sN}$. If $T < C_{sN}$, the manufacturer may seek approval for indication i if $\pi^{iT} > \pi^{jT}$. The movement from both indications to one indication does not change, but the indication for which the marketing approval is sought may change from j to i.

The eliminated indications are the ones with small populations, e.g., orphan drugs, or the ones with high specific costs. The move from seeking approval for both indications to seeking approval for no indication occurs when the quasi-rent for both indications is smaller than the amount of transfer, and the summation of quasi-rents falls into the range of $0 < \Pi_{DVBP}^{bT} < T$. These are the technologies that are marginally profitable for both indications.

4.3.2.3 Information requirement

As shown in the multi-subgroup case, the pricing schemes do not have any effect on the strategy of the manufacturers. As we saw in the multi-indication case, the discrepancy among pricing schemes occurs when the manufacturer targets both patient-types. The cost of validating the marker makes this strategy unattractive for the manufacturer. In the language of game theory, targeting both patient-types is off the equilibrium path for all pricing schemes. Therefore, regardless of the pricing schemes chosen by the payer, the information requirements and also the cost of validating the marker are critical for the manufacturer in choosing which patient-type to target and whether to validate the marker.

In the cases where the marker is validated, marker validation is driven by value-based pricing, not the regulatory approval process. The goal of finding valid marker for regulatory approval purposes happens up to the point where the average value for responders is positive (i.e., equation 2 is satisfied). However, marker validation occurs even when obtaining regulatory approval is guaranteed. Therefore, marker validation is a response to the value-based pricing, not the regulatory approval process. Note that any of the VBP pricing schemes has the same effect.

The choice of when to validate the marker is in many cases not well aligned with social goals: the marker may not be validated even though they would result in better patient outcomes because validating it would reduce profits. The cost of validating the marker is an important

component of the manufacturer's decision on marker validation. Since the manufacturer cannot appropriate any value from the marker validation process, the manufacturer would validate the marker only if doing so increases its profit.

4.4 Conclusion

Value-based pricing schemes are used by many payers as a method of price-setting for health technologies. VBP is perceived to provide the right incentives to innovative companies to invest in the most valuable health technologies. In this chapter I investigate the effect of VBP when a new technology offers the potential to be used for more than one patient-type. When the division of patient populations to be determined exogenously for multi-indication technologies, the payer needs to consider two effects in choosing the pricing schemes: distortion in seeking approval and distortion in the prices of incumbent and future technologies. In such case, the payer has three options to consider for pricing new technologies. MVBP, in which price is set based on the health benefits of the patient-type with the smallest health benefits, is the only pricing scheme that let payer capture a "transfer" from the manufacturer. "Transfer" capturing happens when the manufacturer seeks approval for both indications. However, this pricing scheme brings both distortions. AVBP does not deprive any patient-type from the new technology, though this pricing scheme also brings price distortion for both patient-types. DVBP is the only pricing scheme that does not have any effect on approval seeking of the manufacturers and does not distort price for incumbent and future technologies.

When the division of patient populations is determined endogenously for multi-subgroup technologies, this chapter shows that the pricing schemes do not affect the behaviour of manufacturers in seeking approval and validating the marker. However, value-based pricing by

itself and the cost of validating the marker are the main determinants of the manufacturer's behaviour.

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