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FINANCIAL AND ECONOMIC IMPLICATIONS OF ORPHAN DRUGS THE CANADIAN ECONOMY IN PERSPECTIVE

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Abstract

In a free market, the pricing of prescription drugs is set by supply and demand. Under these conditions, low demand for orphan drugs (drugs used to treat rare diseases) would have prohibitively high prices for buyers and discourage investment in research and development for new orphan drugs by pharmaceutical manufacturers. However, orphan drug legislation designed to encourage the development and distribution of these drugs in various international jurisdictions has supported the financial profitability of the pharmaceutical manufacturing industry. In many developed economies owing to government intervention, health care does not always behave as a normal good. Consequently, these interventions have been made to provide access to orphan drugs while balancing recognition of the investments made in research and development by pharmaceutical manufacturers.

Using Canada as a base case and expanding the analysis to several other developed economies, the authors first demonstrate that currently, there is no legislation to regulate the pricing of orphan drugs in Canada. Accordingly, the financial and economic implications of orphan drug pricing are significant from the perspectives of suppliers and buyers, as well as the federal and provincial governments in Canada, as well as several other countries.

Keywords : Pricing of prescription; prohibitively high prices; Orpham drugs

JEL Classification : D43; H51; I12; O51

Introduction

Orphan drugs are used to treat rare diseases or conditions. While a rare disease is defined by both the prevalence and severity of the condition, the actual definition of a rare disease, and the orphan drug used to treat it, vary by jurisdiction. Serious or/and chronic rare diseases typically have incidences of less than five in 10,000 people, according to the European Commission[1]; in the U.S.A, the **Orphan Drug Act (ODA)** refers to rare diseases as having less than 200,000 total patients

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(Winegarden,[2]). Simoens[3] provides the most exhaustive definition in outlining that a rare disease typically affect fewer than five people per 100,000, is generally life threatening, and causes serious debilitation resulting in a serious chronic condition. Regardless of its definition, the need for orphan drugs cannot be underestimated. Currently, there have been 6,000 to 8,000 rare diseases identified in humans. Health Canada[4] puts the number around the mid-point at 7,000. Many of these diseases tend to be genetic. Approximately one-half of these conditions affect children.

Unlike the broader market for prescription drugs that are used to treat the more prevalent common diseases, the demand for orphan drugs is limited by the small number of patients, given that they are few in number, can often go undiagnosed for long periods of time, and have high mortality rates. This means that the high costs of research and development (R&D) of orphan drugs need to be recouped from a smaller market. Moreover, the financial barriers to entry for new firms into the pharmaceutical industry are quite extensive and high. Accordingly, there are few potential manufacturers of orphan drugs and prices, if left solely to the free market, the cost may become prohibitively high for buyers. Moreover, as the rare disease is not easily identified, the orphan drug may not be covered by health insurance plans, and, if they are, may still be subject to additional approval by the insurance provider. Approval may subsequently be limited to certain specific doses and a predetermined number of refills.

Market Structure

In a free market system, the prices of products are determined by supply and demand, but there may well be various tiers that affect pricing by pharmaceutical companies. With high barriers to entry and comparatively few companies undertaking R&D, oligopolistic pricing is prevalent within certain market segments. When a company is successful in obtaining a patent for a new drug, there may also be monopolistic pricing in other segments until the patent expires. Then, the market for generic drugs reflects a perfectly competitive model, particularly if the drug has been reverse engineered and generic substitutes are available for distribution once the patent expires. There is, however, the potential for competition not based solely on price, but rather by other product attributes or marketing efforts to make a drug appealing to consumers. (Swamy[5])

The pharmaceutical industry is perhaps best examined as an example of a structural oligopoly or domination of the market by comparatively few players. The contributing factors of high R&D costs, patent protection, brand name recognition, and merger and acquisitions (M&A) have reduced the number of competitors and dissuaded new entrants from the market. It should be noted that in an oligopolistic market competition not only is price a consideration but also innovations in the product markets, which occur in the pharmaceutical industry. In addition to new products, firms also present healthcare providers and consumers with enhanced characteristics and upgrades to their existing product mix. The actions of one firm affect other firms and vice versa. Companies earning economic profits have an incentive to keep other firms from entering and capturing a portion of their profits. Pharmaceutical companies spend extensively on innovation in order to gain a competitive advantage in terms of technological and product expertise. Firms make decisions in the context of both existing and potential rivals.

As previously noted, patent protection gives rise to monopolistic pricing for a limited period. Upon expiry of the patent (if not before), competitors often rush to produce generic versions of the drug which moves the price down towards its marginal cost and ends the monopoly status. Firms must, therefore, earn economic profits in excess of accounting profits from the sales, while the patent is in effect; (Swamy[5]) otherwise the company may not be able to remain in business once the patent expires or at least maintain its position as a manufacturer for that particular drug. Following expiration of the patent, product differentiation or

attempts to maintain brand equity/brand loyalty may also be viable strategies for the firm. The net present value of remaining as a manufacturer of that drug must be contrasted with the net present value of abandonment or divestiture of the drug in order to complete a full financial analysis.

Elasticity of Demand, Affordability, the Orphan Drug Act and the Canadian Market

Brewer[6] and BBC News Scotland[7] argue that as the market for orphan drugs is inelastic the high costs of R&D would be shifted unto the consumer and as such some patients would not be able to afford these drugs. Further, the result of non affordability may then discourage additional investment in R&D for new orphan drugs in a perfectly competitive market. To mitigate this problem, the **Orphan Drug Act (ODA) in the U.S.A. was passed in 1983.** The legislation includes tax credits and other preferential policies to encourage the development and marketing of orphan drugs, such as fast-tracking of approval of orphan drugs, grants for new drug development to provide incentives for new orphan drugs manufacturing which should increase the supply and make drugs affordable to those afflicted with rare diseases. In India's case, most patients are forced to pay anything between Rs .60,000 and Rs. 100,000 or more for cardiac drug eluding stents (DEs) though the same stents cost Rs. 28,000 to Rs. 48,000 in European countries and the U.K. where there is price control on a fair pricing mechanism for medical services in sum :

(Drug-eluding stents imported into India by Abbotts Healthcare at Rs. 40.710 each → sold to distributor Sinocare at Rs. 73.446 each → distributor sold at Rs. 1.1 lakh (one lakh = 100000) each to Mumbai-based Hinduja Hospital → patient charged Rs. 1.2 lakh - - a threefold hike over imported price[8].

Further, if a new drug were developed by a competitor for the same affliction, the onus is on the new manufacturer to demonstrate that its product is therapeutically superior Rzakhanov; Meekings, Williams & Arrowsmith[10],. This framework creates a monopoly for pharmaceutical companies to develop a drug for a rare disease when there are no other available therapies (Simoens). Notwithstanding the criticisms relating to market exclusivity and profitability, the ODA has been considered successful from the perspective of increasing the availability of orphan drugs in the United States.

Cohen and Felix[11] in examining orphan drug costs across the United States, England and Wales, and the Netherlands found that orphan drugs had more coverage restrictions than non-orphan drugs with very high per unit costs. In eleven cases the costs were greater than $225,000 USD per year including Myozyme used for the treatment of Pompe disease at $575,000, Cinryze for Hereditary angioedema prophylaxis at $87,000 and Soliris used for Paroxysmal nocturnal hemoglobinuria at $486,000 as the top three most expensive down to Fabrazme for Fabry disease at $239,000 as the example of the eleventh most expensive orphan drug.

In Canada, universal healthcare was introduced in the early 1960s. Since then, basic healthcare costs have been met from public expenditures. As opposed to a normal good in the American system, healthcare functions largely as a public good in Canada. As a consequence, federal and provincial governments play significant roles in regulating the pricing of prescription drugs. Balancing the pricing of drugs in order to sustain universal access to healthcare and yet rewarding pharmaceutical manufacturers for R&D investments are economic challenges.

Prelude

Orphan drugs pricing according to free market

Setting the prices of orphan drugs, while following market-oriented economic principles, is not always reflective of supply and demand as the market forces have been altered by the presence of financial incentives provided by legislative means. While basic demand and supply relationships are outlined in this study, various other pricing paradigms are examined in tandem.

Demand

First, it must be understood that regardless of the rare disease under consideration, these patients account for a small percentage of the total population; therefore, the demand for any orphan drug will by definition be less than a more commonly prescribed medicine. Winegarden estimated that the total cost for patients in the United States with rare diseases in 2011 was in the vicinity of $186.6 billion. The National Health Expenditure Accounts published figures showing that total national healthcare expenditures in 2011 reached $2.5 trillion, including the cost of dental care. Expenditures for rare diseases accounted for 7 per cent of the total national American healthcare expenditures. Recall from previous discussion that the maximum size for a rare disease is less than 5 per cent of a population or 200,000 cases in total. Consequently, the 7 per cent spent on rare diseases is higher than the expenditure on non-rare diseases.

Second, orphan drugs are characterized by relatively inelastic demand by the patients with rare diseases. The description by the European Commission outlines the characteristics of rare diseases as "life-threatening, seriously debilitating, or serious and chronic" (CORD[12]). Patients with rare diseases have to rely on the orphan drugs to either stay alive or enjoy some minimal quality of life. Therefore, no matter what the price, patients or their parents/guardians typically would be willing to purchase the orphan drug. Forman, et al.[13] have argued for a worldwide policy/action for rare diseases, while Gratzer[14] made the same case for Canada.

Finally, approximately 300 orphan drugs have been approved for sale within the last 25 years despite the identification of up to 8,000 rare diseases (Sharma, et al,[15]). Currently, there are 1,100 new projects for rare diseases at various stages of development (Largent and Pearson,[16]). In other words, numerous patients with various rare diseases have no drugs available for their conditions and, more importantly, for many diseases, there are no drugs in the development stage. The demand for orphan drugs is largely unsatisfied by the current supply pipeline.

Although the ODA sought to meet the demand for orphan drugs, the development of new drugs may have taken place through increased risk to the patient. Under usual testing protocols, the pharmaceutical company is required by the Food and Drug Administration (FDA) to establish clear evidence of drug efficacy and safety before a drug is marketed to the public. The usual process would involve conducting controlled trials (usually randomized) comparing the potential drug to placebos or existing treatments. However, with the low prevalence of the rare disease and the urgency for the drug, the FDA is empowered to waive certain criteria at its discretion. This right is often exercised in the case of orphan drugs, due to the challenges encountered in trying to conduct robust clinical trials in such small populations (Kesselheim, et al.[17]). Consequently, there is a great demand for orphan drugs, many of which are simply not met and concerns that required testing may have been cut in attempting to meet the demand.

Supply

On the supply side, the discovery and development of new drugs either for rare diseases or common diseases are difficult and complex. Clinical trials are expensive and represent a significant barrier to full drug approval. Previous studies estimated the general total cost of a new successful orphan drug was $1.2 billion, which included the various costs of previous failed attempts DiMasi and Grabowski,[18]. However, Herper[19] suggested that $1.2 billion was too low. According to Herper, the range of expenditures for R&D is significantly larger. For example, AstraZeneca claimed expenditures of $12 billion on the R&D of every new drug, whereas Amgen claimed spending $3.7 billion. Although Herper reported R&D expenditures for all drugs, it may be inferred that the R&D costs of orphan drugs would probably not be less than $1.2 billion. The risks of failure for each clinical trial are high. Eventually the costs of failed trials are added into the total costs and passed to the buyers of other

drugs. In drug approval, orphan drugs are often handled differently than drugs for more common diseases.

Given the high attrition rate of drug development, orphan drugs are a riskier business venture than seeking new medicines for more prevalent diseases. The high costs of R&D, long lead times to market, legal restrictions and protection of intellectual property rights by patents, all act as barriers to entry of new manufacturers, and could well result in negative net present values. Clinical trials in particular require lengthy time periods before government agencies approvals, which has the effect of accruing significant expenses before earning income from sales, sometimes 10-15 years, which may be beyond an acceptable payback period. These accrued expenses are large opportunity costs which can discourage investment in R&D for other drugs that may have both higher and more immediate return on investment.

Patent protection can be a barrier to supply, because it can limit the large-scale production of new orphan drugs by competitors. In some countries, competing generic pharmaceutical manufacturers pay licensing fees to patentees in order to sell orphan drugs; often the fees are high and leave low margins. Because orphan drugs are aimed at a small market, the motivation to purchase patents or license products is weaker than other prescription medicines. An example of the inaccessibility of orphan drugs for patients under pricing in the free market system is illustrated by Gaucher disease, which is a genetic disease having a prevalence of 1 in 100,000 people. The average treatment cost for Gaucher disease patients can reach $200,000 per year (Grabowski[20]), which for many patients will be unaffordable and so they forego treatment.

With reduced opportunities for gaining large profits from blockbuster drugs used to treat more prevalent diseases, the pharmaceutical industry has refocused their attention on more niche markets, such as rare diseases and personalized medicines.

Legislation for Orphan Drugs: The Experience in the U.S.A. and European Union

The 1983 ODA was the first legislation related specifically to orphan drugs. This Act was intended to motivate the major research-based pharmaceutical manufacturing companies to develop new medicines in exchange for exclusive marketing rights, tax credits, government subsidies for research, and fast-track market approval processes. In 2000, similar legislation was passed by the European Commission to provide incentives to the orphan drugs industry in the European Union. Both pieces of legislation add additional years of market exclusivity on top of patent rights (**Table 1**). During these periods, no similar products are allowed to enter the market, which aims to guarantee the profitability of companies manufacturing orphan drugs. These acts also provide tax credits based on clinical trial expenditures (up to 50 per cent in the U.S.), and establish research grant programs for public sector (National Institutes of Health) and private foundations conducting research in orphan diseases (Winegarden; Sharma, et al,). Finally, to speed up the time to market orphan drugs, these

TABLE 1
ORPHAN DRUG LEGISLATIONS IN U.S. AND E.U.
Adapted from Sharma, et al,[15]

	U.S.A.	E.U.
Legal Policy	Orphan Drugs Act (1983)	European Commission: Regulation (EC) No 141/2000
Marketing Exclusivity	7 years	10 years
Tax Credit	50% for clinical studies	Managed by the member states
Grants for Research	Available	Available
Accelerated marketing procedure	Yes	Yes

governments have established fast-track review and approval processes. In the 10 to 15 years after the American and EU legislations, there has been a trend of increased numbers of orphan drugs approved for sale by approximately 10-times in the EU (European Medicines Agency,[21]) and 20-times in the U.S.A.

Profitability of the Pharmaceutical Industry

Pharmaceutical companies are those companies involved in the manufacture and marketing of drugs. Three categories of pharmaceutical companies in Canada are: subsidiaries to foreign companies, generic companies and small biotechnological companies and subsidiaries to foreign companies hold a large share of the market and produce brand name drugs[22]. Many of these companies are headquartered in the U.S. or other countries. Small biotechnology companies are smaller-sized entities with roughly two drugs in the market. Generic companies produce drugs that are marketed after patents expire on various medicines. Pharmaceutical companies, like any other for-profit business, earn net income by selling sufficient product to cover costs and earn a return on investment. However, the nature of the pharmaceutical industry is unlike other industries as human lives are directly at stake. As a result, firms in the pharmaceutical may face greater scrutiny in conducting their business operations. Profit margins of roughly 17 – 18 per cent among pharmaceutical companies, which made the **Fortune 500 list**[23], do not go unnoticed (Moser,[24]; see **Fortune 500 2013** : full list at money.cnn.com). There are many public accusations that pharmaceutical industry earnings are excessive when compared with other industries[25]. However, Moser pointed out that, if the high costs incurred for R&D by pharmaceutical companies are factored in, the profits margins of the pharmaceutical industry are comparable to banking, tobacco and real estate on a risk-adjusted basis. Interestingly, 13 of the Fortune 500 list were listed as Pharmaceutical Companies in 2013.

In 2011, net revenues from pharmaceutical and medicine manufacturing in Canada were $1.1 billion, which was a 36 per cent increase over 2010, but still less than the $1.5 billion profits of ten years ago (Industry Canada[26]). Wholesaler-distributors (**Table 2**) of pharmaceuticals and pharmacy supplies have more than doubled their operational budget by maintaining a compound annual growth rate of 7.1 per cent (Industry Canada[27]).

The **Orphan Drug Report released by Evaluate in April 2013** provided sales and ROI forecasts for the orphan drug market over the next five years. The **Report** predicts that orphan drug sales will experience an annual compound growth rate of 7.4 per cent from 2012-2018 with global sales projected to reach $127 billion by 2018, which is almost double the usual prescription drug market. The report also estimated that orphan drugs will provide 1.7 times

TABLE 2
NET REVENUES FOR PHARMACEUTICALS AND PHARMACY SUPPLIES
Wholesaler-Distributors (NAICS 41451) in Canada
Modified from Industry Canada (2013b).
CAGR, Compound Annual Growth Rate.

Category	Value in $ Billion		CAGR	% Change in
	2002	2011	2002-2011(%)	2010-2011 (%)
Total Operating Revenue	24.2	44.9	7.1	3.5
Total Expense	22.7	42.4	7.2	1.7
Net Revenue	1.5	2.5	5.8	47.0

the ROI of non-orphan drugs for those that make it to phase three (the final phase) of clinical trials. Further, the developmental costs for drugs in phase three are approximately one-half of non-orphan drugs, which is largely due to the smaller populations that are available for testing[28].

A review of the costs associated with orphan drug discovery demonstrates that the discovery process is an economically viable activity (Meekings, et al.,). These authors demonstrated that compared to non-orphan drugs, orphan drugs have shorter clinical trials and greater success rates in regulatory filings. Consequently, the time to market is shorter. With additional tax credits and longer time for protection of the discovery of the drug, costs are lower and revenues can be higher, which in tandem results in larger ROIs being achieved.

Lastly, while orphan drug status creates the opportunity for pharmaceutical companies to quickly market their product at a premium price, there are no measures in place preventing these orphan drugs, which are intended to be used for rare diseases, from being used off-label for other rare diseases or more common conditions (London,[29]). Kesselheim, et al. examined four top-selling orphan drugs (Lidoderm, Provigil, Sensipar, and Gleevac) and demonstrated that the rate of growth in usage of these drugs for non-orphan conditions was greater than the intended orphan usage. This phenomenon is referred to as "indication creep." This is problematic as no new clinical trials are conducted for these prescriptions which are written for the non-intended use of the drug. Accordingly, the full effects of the drug therapy are not known, including the benefits of obtaining additional data on the efficacy of the drug through registered clinical trials. Hughes-Wilson, et al[30], argue that an orphan drug, which becomes a best seller as a result of this additional use, should lose its orphan drug status, and hence the benefits enumerated under the ODA. This condition may well be to the detriment of the original target market/ user of the orphan drug which required its development in the first place.

The approaches to price setting of orphan drugs in Canada would certainly be expected to impact the profitability of the pharmaceutical industry. In the U.S., where the free market sets prices for drugs, the ODA has been seen as providing a competitive advantage for companies that conduct research to discover and produce these drugs. Specific examples of this advantage were reported by Meekings, et al. who studied 86 orphan drugs and 291 non-orphan drugs. This study of orphan versus non-orphan drugs, which were marketed between 1990 and 2010, found a 25.8 per cent compound annual growth rate (CAGR) for orphan drugs compared to 20.1 per cent for non-orphan drugs. This trend was projected by these authors to continue to the point where the total mean revenue generated by orphan drugs would be at par with that of non-orphan drug by 2030. So, orphan drugs have not only become profitable, but are now more profitable as a result of the ODA.

Market Entry and the Cost of Production

The prescription pharmaceutical market is a highly concentrated oligopoly. Typically, the large pharmaceutical manufacturers, which have been getting even bigger as a result of M&A activity in the past two decades, have invested heavily in R&D. In the U.S., before a drug enters the market, it goes through three stages of clinical trials at the end of which a New Drug Application (NDA) is submitted to the FDA (Reiffen & Ward,[31]). At the expiration of the patent for brand name drugs, generic drugs can join the market. For a generic drug to join the market, the generic drug company, is required to submit an Abbreviated New Drug Application (ANDA) to the FDA. The FDA is charged with determining if the generic product is the bioequivalent of the original patented drug and Prior to the passage of the Wixman-Hatch Act, a more rigorous procedure was required for generic drug approval.

On average before a drug was approved in the 1990s in the U.S., it cost the pharmaceutical companies $335 million to develop the drug and roughly $467 million to conduct clinical trials. This amounts to a

total of roughly $802 million of total implicit and explicit cost. The average total cost for generic drugs in the U.S. reduced significantly from $600,000 to roughly $330,000 upon passage of the Waxman-Hatch Acts. In Japan, the average cost of a drug to the brand company is between $182 million to $243 million in current US dollars (¥15- ¥20 billion) (Iizuka,[32]). The corresponding cost for generic companies ranges from $364 thousand to $1.3 million (¥30- ¥100 million)(Iizuka, 2009). These numbers should be viewed relatively, as later studies put the cost for making specific drugs in the billions as outlined earlier (DiMasi and Grabowski; Herper,). The high costs of drug manufacturing make the pharmaceutical industry highly concentrated and difficult to enter.

Iizuka studied the factors that affected the generic drug entry into the market, once patents expired in Japan. The study indicated that entry depended on: the potential market size, the level of vertical integration of institutions that supplied and dispensed drugs, and the sizes of hospitals that prescribed brand name prior to patent expiration. The finding regarding market size was consistent with prior studies conducted in the U.S. where there was greater entry of generic drugs in larger markets (Morton,[33]). This was expected because a generic drug company will be able to cover their costs, when there is a potentially large demand for the drug. It is important to note that generic companies do not know the number of competitors that will enter the market beforehand. Iizuka's second finding was that fewer generic entries were observed, when a large proportion of the market was not vertically integrated (separate prescribing and dispensing institution). The proposed explanation was that in an integrated market, organizations would take advantage of high profit markups offered by newer generics, which was a characteristic unique to the highly regulated Japanese market.

Interestingly, in contrast to the findings in the U.S., fewer generic companies entered the market, when the brand name was mainly used by large hospitals in Japan (Iizuka ; Morton,). This market observation was attributed to a healthcare trend created by physicians and surgeons in Japan, especially those graduating from large institutions then working with hospital departments of the same institutions. These graduates followed institutional guidelines, which insisted on prescribing branded over generic drugs. This circumstance ensures more success for branded drug and more risk for generic companies that may consider joining the market. Generic drugs generally held a larger portion of the market in U.S. and U.K. of 53 and 54 per cent, respectively, when compared to the highly regulated Japanese market, in this case 16.8 per cent between 2003 and 2004.

Implications of Government Interventions in Drug Pricing in Canada and Other Developed Countries

In Canada, pharmaceutical manufacturers, wholesalers, and retailers operate to maximize profit within the constraints of the not-for-profit public health care sector, which is guided by a principle of universal access to hospital care and funded by government spending. The federal government makes transfer payments to each provincial government, which is responsible for paying for public health services, hospital care, and provincial drug plan programs. In 2008, pharmaceutical expenditures represented 1.8 per cent of Canada's GDP (PMPRB,[34]). The split jurisdictional responsibility for health care means that pharmaceutical drug pricing can create friction between other federal and provincial governments' policies (Rosenberg-Yunger, et al.,[35]). For example, industrial policy at the federal level attempts to draw R&D investment to Canada by creating economic conditions that allow for profitability and protect intellectual property rights, such as patents, whereas the provincial governments attempts to control drug costs may involve imposing higher taxes, which creates further disincentives for innovation, especially for R&D of orphan drugs (Seoane-Vazquez, et al.,[36]).

Based on 2010 data, prescription drugs have become the second largest component of health care costs in Canada (Daw and Morgan,[37]). To control costs at the provincial level, each provincial

government establishes a formulary, which is a list of the drugs that will be reimbursed to hospitals and to provincial drug plans that provide coverage to seniors, and individuals receiving social assistance or needing help with very high drug costs. Provincial hospitals and pharmacare programs are the largest payers for prescription pharmaceuticals. Private insurers, the federal government (for Aboriginal, RCMP, and retired military veterans), and uninsured/partly insured individuals are the remaining buyers. The provinces are informed about all drugs which should be considered as eligible for listing in formularies through the Common Drug Review, following an evaluation of safety, efficacy, and cost-benefits by Health Canada (the federal government department in Canada that is responsible for setting national health standards). Provincial governments typically negotiate directly with manufacturers, but some hospitals have moved to negotiating with third-party wholesalers.

There is evidence that the provincial governments do not work together on setting formularies and reimbursement costs, but actually undermine the efforts of each other. There is an information asymmetry in negotiation which can induce moral hazards into the negotiation process. For example, some provinces have set "most-favored nation" policies that require manufacturers to offer them the lowest price in the country (Grootendorst and Hollis,[38]), and yet there is no requirement to disclose that these negotiations have taken place, let alone the results of the negotiation. In addition, provinces having more power, such as Ontario (largest province in terms of population, GDP and government expenditure on health care) will publicly list nominal high prices that are in fact partially reimbursed by manufacturers, but hidden by confidentiality agreements. This competition and lack of transparency among the provinces leaves vulnerable uninsured and smaller institutional buyers facing the nominal high prices (Anis,[39]).

The provincial drug plans use several general approaches to price setting, including exclusion of substitution, e.g. one choice, no options, reference-based prices, and lowest cost tenders and bargains. There is no one specific policy regarding orphan drugs in Canada across federal and provincial boundaries (Daw and Morgan,). For orphan drug pricing in the U.K., which like Canada provides publicly funded health care, reference-based pricing is used to approve reimbursement of prescription drug costs to hospitals. In the U.K. system, approved orphan drugs cannot exceed a price threshold of £ 25000 - £ 30000 per Quality-Adjusted Life Years (QALY) gained (Drummond et al.,[40]).

The traditional approach in the US is to allow pricing for prescription drugs to be whatever the market can bear so one result is that drug plans tend work on a cost-sharing basis between insurer and insured without any restriction to access; however, if the prices are considered too high, then patients forego purchasing the prescription medicines. There are limited circumstances when a Canadian physician can apply through the Special Access Program (SAP) at Health Canada to have a prescription drug that has been approved for use outside of Canada to be purchased and imported into Canada for restricted usage, i.e. compassionate or emergency cases where conventional treatment has failed (Health Canada, 2008). Since the provinces will not reimburse the buyers of drugs that are not listed in the formularies, the costs for these prescription drugs are usually the sole cost responsibility of the patient. Note below the creation of different financial ratios and metrics to account for the uniqueness of financial data within the pharmaceutical industry or by government.

The Canadian Patented Medicines Prices Review Board (PMPRB) is responsible for ensuring that the "factory gate" price is not excessive; however, the Board has no control over drugs acquired through the SAP, and it cannot regulate generic drugs, wholesalers, retailers, or pharmacists' professional fees. The PMPRB uses a reference-based pricing that compares the median drug prices in seven other countries (U.S., U.K., France,

Germany, Switzerland, Italy, and Sweden) and as mandated by the Patent Act, keeps track of pharmaceutical industry trends including the ratio of R&D expenditures to sales by patentees. According to the PMPRB's interpretation of Canada's patent regulations, R&D expenditures are costs that would have qualified:

> ...for an Investment Tax Credit for scientific research and experimental development under the provisions of the *Income Tax Act* that came into effect on December 1, 1987. By this definition, R&D expenditures may include current expenditures, capital equipment costs and allowable depreciation expenses. Market research, sales promotions, quality control or routine testing of materials, devices or products and routine data collection are not eligible for an Investment Tax Credit and, therefore, are not to be included in the R&D expenditures reported by patentees. (PMPRB,[34])

For more than 15 years, the overall pharmaceutical R&D-expenditures-to-sales ratio has been declining in Canada, and this ratio has remained below 10 per cent for the past eight years, despite public commitments made over 25 years ago by members of the industry; although to be fair, there is a large dispersion among the firms. Nevertheless, only Italy has experienced a worse pharmaceutical R&D to sales ratio between 2000 and 2008 among the historical comparative group countries mentioned above.

Prices of all patented prescription drugs are reviewed semi-annually with consumer price index (CPI) changes taken into account relative to the comparative groups. The PMPRB relies on voluntary compliance by the pharmaceutical manufacturers to follow the approved prices and has quasi-judicial powers to impose fines, as well as to order lower prices to offset excessive revenues that have been collected by the offending companies. From 1993 to present there have been about 80 voluntary compliance undertakings by patentees. It is unclear whether there has been more vigilance of the industry in later years, but the trend has been that most of the undertakings have been ordered within the past five years.

Clearly, the choice of the reference comparisons will be a critical element for evaluating whether prices are considered as excessive; choosing is doubly complicated when considering orphan drugs, which are unlikely to be used in all jurisdictions and may be unique one-of-a-kind medicines. In addition, patent protection rights provided in various countries legal systems can impact the allowable prices in these other jurisdictions (competition from generics where patent rights are weaker) and have been known to change over time. According to the PMPRB (2010), the Foreign-to-Canadian price ratios for prescription patent drugs are higher in Switzerland, Germany and U.S., but lower in UK, France, Germany, and Sweden. Interestingly, there were no obvious correlations reported between the R&D-to-sales-ratios and the prices for patented medicines relative to Canadian prices, using the same sets of data. In fact, the patented medicine prices in France were 10 per cent lower compared to Canada and the R&D-to-sales ratio was double the ratio in Canada[32]. However, there are significant barriers to entry (e.g. human and financial capital) into the market of orphan drugs for pharmaceutical manufacturer. Rewarding pharmaceutical R&D by allowing profitable price setting and yet balancing this recognition with the need for financial sustainability of payers has been an on-going policy struggle for governments.

As mentioned earlier, the broad market for prescription pharmaceuticals is an oligopoly; however, orphan drugs legislation can create protected monopolies for pharmaceutical companies. Creating monopolistic markets would seem to be incongruent with providing sustainable public funding for pharmacare in Canada, especially given the poor correlation between R&D and sales of patented medicines outlined previously. However, coordinated bulk-

purchasing by the provinces and subsidizing drug R&D, especially basic research and clinical trials (free of political influence), are possible policy levers that may more easily be implemented with orphan drugs than other prescription medicines. At the same time, it should not be forgotten that there are opportunity costs associated with government paying for orphan drugs, which can be viewed as a form of personalized medicine of limited benefit for a small population. For example, the investment in providing orphan drugs to a small number of patients could be used instead in a larger number of patients with more effective treatments.

Conclusions

In October 2012, the Government of Canada announced its intention to create a national framework, which includes a patient registry of all rare diseases in Canada, to improve access to treatments for rare diseases. Registries of rare disease can be good sources of cost-effectiveness data and, therefore, are good steps forward in the discussion about orphan drugs price policies in Canada. Ensuring the economics of orphan drug policies are sustainable will depend on shared strategies from pharmaceutical manufacturers, federal, and provincial governments in Canada.

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