

# The Effect of Evidence-Based Drug Coverage Policies on Pharmaceutical R&D: A Case Study from British Columbia

Effet, sur la R&D pharmaceutique, des politiques  
d'assurance-médicaments fondées sur des preuves :  
une étude de cas de la Colombie-Britannique



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## Abstract

**Background:** To manage public expenditures in the mid-1990s, British Columbia implemented evidence-based drug coverage policies, including “reference pricing.” Industry lobbied against the province’s policy, arguing that reference pricing harms patients and that it is inconsistent with federal and provincial legislation. Researchers and the courts have studied and rejected industry’s claims. However, industry also threatened to halt R&D investment in British Columbia and continues to so threaten other provinces contemplating evidence-based drug coverage policies. The purpose of this study is to review evidence regarding these threats.

**Methods:** Provincial-level R&D data for 1988–2006 were used to analyze the impact of BC PharmaCare’s policies on pharmaceutical R&D in British Columbia. We used statistical analyses to determine whether the province’s policies affected BC-based R&D as expressed in two ways: (1) as inflation-adjusted expenditure per capita in British Columbia and (2) as the ratio of expenditure per capita in the province over expenditure per capita in the rest of Canada.

**Results:** Evidence-based drug coverage policies had no statistically significant negative effects on BC-based pharmaceutical R&D. BC R&D was slightly above expected trends in 1997 and slightly below expected trends in 1998 and 1999 (though not statistically significantly in either case). From 2001 to 2003, BC R&D was (statistically significantly) above expected trends.

**Conclusions:** While they are part of the politics of the pharmaceutical sector, claims and threats regarding connections between coverage policy and location of R&D investment are not borne out in British Columbia’s experience. This is likely because, as suggested by business and economic literature, firms locate R&D based on the expected cost-to-firm and productivity of the R&D investment itself. Prudent policy would therefore manage pharmaceutical expenditures using evidence-based policies and pursue scientific and economic development goals through direct and strategic government investment in local scientific capacity.

## Résumé

**Contexte :** Afin de gérer les dépenses publiques au milieu des années 90, la Colombie-Britannique a mis en œuvre des politiques d’assurance-médicaments fondées sur des preuves – y compris l’établissement du coût en fonction du produit de référence. L’industrie s’est élevée contre la politique de la province, soutenant qu’elle était nuisible pour les patients et qu’elle contrevenait aux lois fédérales et provinciales. Des chercheurs et des tribunaux ont examiné puis rejeté les revendications de l’industrie. Toutefois, cette dernière a également menacé de mettre fin aux investissements en R&D en Colombie-Britannique et continue de menacer d’autres provinces qui envisagent d’adopter des politiques d’assurance-médicaments fondées

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sur des preuves. La présente étude vise à examiner les preuves relatives à ces menaces. **Méthodes :** Des données provinciales en R&D pour 1988–2006 ont été utilisées pour analyser l'incidence des politiques d'assurance-médicaments de la Colombie-Britannique sur la R&D pharmaceutique dans la province. Nous nous sommes servis d'analyses statistiques pour déterminer si les politiques de la province influençaient la R&D en C.-B. – la R&D étant exprimée de deux manières : (1) les dépenses par habitant ajustées en fonction de l'inflation en Colombie-Britannique et (2) le rapport des dépenses par habitant dans la province et des dépenses par habitant dans le reste du Canada.

**Résultats :** Les politiques d'assurance-médicaments fondées sur des preuves n'ont pas eu d'incidence négative statistiquement importante sur la R&D pharmaceutique en C.-B. La R&D dans cette province dépassait légèrement les attentes en 1997 et était légèrement en deçà de celles-ci en 1998 et en 1999 (bien que ces différences fussent statistiquement négligeables dans les deux cas). De 2001 à 2003, la R&D en C.-B. a dépassé les attentes, et ce, d'une manière statistiquement significative.

**Conclusions :** Bien qu'elles fassent partie de la politique du secteur pharmaceutique, les revendications et les menaces concernant les liens entre les politiques d'assurance-médicaments et l'emplacement des investissements en R&D ne se sont pas corroborées par l'expérience de la Colombie-Britannique. C'est probablement parce que, comme le suggère la documentation économique et industrielle, les sociétés choisissent l'emplacement des projets de R&D en fonction des coûts prévus et de la productivité des investissements en R&D proprement dits. Une politique prudente permettrait donc de gérer les dépenses pharmaceutiques avec des politiques fondées sur des preuves, et de poursuivre des objectifs scientifiques et de développement économique grâce à des investissements gouvernementaux stratégiques dans les capacités scientifiques locales.

**G**OVERNMENTS AROUND THE WORLD STRUGGLE WITH THE NEED TO MANAGE pharmaceutical expenditures in ways that provide equitable and sustainable access to necessary medicines. They are also mindful that the pharmaceutical industry is a major sector for economic and scientific activities (Jacobzone 2000; Morgan et al. 2008). In the 1990s, BC PharmaCare – the public drug plan in British Columbia – began to manage public expenditure on pharmaceuticals using a series of coverage policies focused on paying only for scientifically established health outcomes (Morgan et al. 2004). These policies are best represented by BC PharmaCare's reference pricing policy, which limits public subsidies for drugs in select classes based on the price of lowest-cost alternatives within those classes.

Industry strongly opposed BC PharmaCare's approach to coverage policy and, in particular, the use of reference pricing. Manufacturers launched advertising campaigns

suggesting that reference pricing would have negative effects on patient health and the healthcare system. They also initiated a lawsuit challenging the policy's legality (Courts 1995; Mullens 1997; Brunt et al. 1998). Several independent research studies and the BC courts have vindicated government on these counts (Grootendorst and Holbrook 1999; Hazlet and Blough 2002; Morfitt et al. 2002; Schneeweiss, Soumerai et al. 2002; Schneeweiss, Walker et al. 2002; Schneeweiss et al. 2003, 2004). Industry also argued that British Columbia would lose on investment because BC PharmaCare's policies were "unfriendly" towards patented pharmaceutical manufacturers. This contention has been less thoroughly investigated and is the subject of this paper.

Manufacturers claim that "drug policy and economic development are indissociable" (Williams 2006). There would seem to be an intuitive appeal to this reasoning: why would firms develop drugs in a region that was not going to pay top dollar for them? The initial costs of drug development are very high and the chance of success relatively low, suggesting that rewards to products that come to market must be significant and certain in order for firms to undertake research. If local drug coverage policy does not provide the promise of future sales and profits in the region, companies might have little incentive to invest in local R&D. We tested this logic by studying pharmaceutical R&D investment in British Columbia for a span of time (1988–2006) predating BC PharmaCare's use of evidence-based drug coverage policies until after these policies were well established. We discuss the findings in the context of literature on the determinants of business decisions concerning R&D location.

## Pharmaceutical Policy in Context

Pharmaceuticals are developed and sold in a highly regulated market fraught with imperfect information, regulatory interventions and limitations on competitive activity. First and foremost, pharmaceutical innovations rely on information, or "ideas," which are ultimately public goods that may be very expensive to produce yet relatively inexpensive to replicate. A perfectly free market for such ideas would result in almost certain market failure: however valuable they may be, no firm would have an incentive to invest in the production of new ideas that others could readily copy. Policy makers therefore grant pharmaceutical inventors temporary market power through patent protection in an attempt to make innovation profitable.

Second, the products generated through pharmaceutical R&D are not conventional consumer goods; they are potent inputs into healthcare. Further, the impact of a medicine on a patient's health status is often difficult to determine owing to the complexity of human biology and pharmacologic activity. Policy responses to these unique characteristics include the regulation of drug production, marketing and even retailing, as well as the legal requirement that consumers cede decision-making authority over product selection to a learned intermediary, physicians who are licensed to prescribe medicines.

Finally, the demand for medicines is associated with poor health status, which is often concentrated among a minority of individuals. Often too, those with the greatest needs for medicines are also those with the least ability to afford them. To spread the financial risk associated with ill health, public and private insurance programs finance pharmaceutical purchases for various groups of beneficiaries. These programs can improve access to medicines among those covered, but they can also distort the financial considerations of patients and their prescribing doctors.

Policies relating to pharmaceutical cost control are situated in this unique, complex context. Simply letting the market work to determine prices through consumer demand and competitively determined supply isn't feasible because of the many layers of regulation, market distortion, patent protection and price-insulated consumers. Some level of intervention may be needed to equalize the market power of sellers and buyers, to improve the level of information about products or to adjust the financial incentives of those making purchasing decisions (patients and their prescribing doctors).

## Drug Coverage Policies of BC PharmaCare

The BC PharmaCare program began a concerted effort to control the costs of drugs in the early 1990s. Prior to this period, BC PharmaCare had been providing seniors and social assistance recipients nearly full coverage at prevailing drug prices for virtually all drugs licensed for sale in Canada (Morgan et al. 2004). The result was extraordinary expenditure growth that provoked a formal review of the BC PharmaCare program in 1993 (British Columbia 1993). The review suggested that the system was unsustainable and that costs would either have to be shifted to consumers by reducing benefits, or better managed through new cost-control mechanisms. Government opted to try expenditure management, influenced in part by evidence showing that much of the cost growth under BC PharmaCare was due to increasing use of newer drugs that were more expensive than older, comparable medicines (Anderson et al. 1993). This potentially wasteful situation was possible because neither the insured patient nor the prescribing physician had any incentive to consider the relative price of two drugs in choosing treatment.

Starting in 1994, BC PharmaCare began limiting the amount it would pay towards the purchase of brand-name drugs if equivalent generic alternatives were available. Unlike no-name consumer goods, generic drugs are virtually identical to brand-name products; they are licensed by Health Canada on the basis that they are chemically equivalent to the original drug (Health Canada 2006). British Columbia's new policy would limit government subsidies to an amount equal to the price of the generic drug, giving patients an incentive to consider the cost of brand-name products when choosing their treatment. The policy had three possible outcomes: (1) brand-name firms could compete on price with generics and therefore become fully subsi-

dized, (2) patients could pay the price difference if they preferred the brand enough to “top up” for it, or (3) patients could receive the generic substitute fully subsidized. Evidence suggests that the last outcome prevailed swiftly and in virtually all cases (Grootendorst et al. 1996; Morgan 2002).

Also in 1994, the BC Ministry of Health established the Therapeutic Initiative (TI) to assist with drug coverage decisions for new, patented drugs – those for which no generic options were available. The TI is a university-based advisory body of academics and health professionals who evaluate scientific evidence concerning the comparative clinical safety and effectiveness of pharmaceuticals for which manufacturers seek public coverage (Morgan et al. 2004). Evidence, critically appraised by the TI, would form the basis of BC PharmaCare’s coverage policy towards patented drugs. On advice from the TI, BC PharmaCare applied its evidence-based decision-making framework through the implementation of a reference pricing policy to three drug classes in 1995: nitrate drugs, histamine-2 blockers and nonsteroidal anti-inflammatory drugs (NSAIDs). Two additional classes were added in 1997: angiotensin-converting enzyme (ACE) inhibitors and calcium-channel blockers. A panel of experts identified these categories because there was a lack of scientific evidence, suggesting that the products within them were differentiated in systematic and clinically meaningful ways.

Under reference pricing, BC PharmaCare limited the subsidy provided for medicines in these classes to the price of low-cost options within them. As with the generic pricing policy, manufacturers could compete on price (and therefore be fully covered), patients could pay the difference in price for preferred brands or they could switch to a fully covered product. The policy exempted patients with valid clinical reasons for receiving a particular product. Moreover, any product would be exempted from the policy if the manufacturer could provide scientific evidence to substantiate claims of superiority in terms of clinically relevant patient health outcomes. The burden of proof under these evidence-based coverage policies therefore rests with manufacturers; to date, none has met this requirement in the drug classes to which BC PharmaCare applies reference pricing.

## **Industry’s Response to BC PharmaCare’s Policies**

The pharmaceutical industry implemented three strategies to counter BC PharmaCare’s reference pricing policy. The first was a public relations campaign aimed at swaying public opinion and thereby curtailing political support for the policy. Manufacturers’ anti-policy advertisements claimed the BC government was putting cost-cutting ahead of patient health (Brunt et al. 1998). Public buy-in appeared low, as the majority (71%) of seniors perceived that industry’s motivation was lost sales; just 8% thought reference-based pricing was “bad policy” (Brunt et al. 1998). Seniors, in particular, generally supported the government’s program, with the highest level of

support among those who knew the most about the policy (Chappell et al. 1997).

Research would later provide evidence in support of the policy. Independent research groups at Harvard, McMaster University and the University of Washington found that reference pricing had little impact on health services utilization – it temporarily increased physician billings during a three-month period surrounding the policy’s implementation – and that it did not produce negative health impacts (Grootendorst and Holbrook 1999; Hazlet and Blough 2002; Morfitt et al. 2002; Schneeweiss, Soumerai et al. 2002; Schneeweiss, Walker et al. 2002; Schneeweiss et al. 2003, 2004). Studies have, however, shown that British Columbia’s reference pricing policy reduced drug expenditures on the classes of medicines to which it was applied. A formal government review of all available evidence estimated that total savings generated by reference pricing in the province would be \$76 million from 2001 through 2010 (Morfitt et al. 2002).

The second component of the industry’s response to BC PharmaCare’s reference pricing policy was to challenge the policy on legal grounds. In December 1995, two months after reference pricing began, the Pharmaceutical Manufacturer’s Association of Canada (PMAC, now called Canada’s Research-Based Pharmaceutical Companies, or Rx&D) and seven member companies filed a suit against the provincial government. They argued that reference pricing was inconsistent with existing federal and provincial legislation and based on inappropriate consideration (Coutts 1995). The case was dismissed by the BC Supreme Court in June 1996 and by the BC Court of Appeals in August 1997 (Mullens 1997).

The third industry tactic was to threaten to withdraw research investment from British Columbia as long as reference pricing was applied. Such threats continue to be used when reference pricing enters policy discussions in other parts of the country (Urquhart 2005; Rx&D 2006). In response to the suggestion of reference-based pricing as a policy possibility in Ontario, Rx&D suggested “we must be careful that Ontario remains competitive in the world and does not create policies that inhibit Ontario’s ability to attract R&D investments” (Rx&D 2006). During recent discussions of possible drug policy changes in Quebec, Rx&D argued that “to ensure the strength of the industry, we believe there must be total synergy between drug policy and Quebec’s economic policy, which also relies on a strong, innovative pharmaceutical industry generating high quality jobs” (Williams 2006). The message is clear: if your province adopts reference-based pricing (which hurts our profits), we’ll punish you by taking away investment (and the corresponding jobs and indirect economic benefits).

To our knowledge, the impact of British Columbia’s reference pricing on local R&D activity has not been thoroughly examined.

## Pharmaceutical R&D in Canada, 1988–2006

To understand recent trends and levels of pharmaceutical R&D in British Columbia, it is necessary to review the Canadian history with respect to pharmaceutical patents and R&D (Grootendorst and Di Matteo 2007). Prior to the late 1980s, pharmaceutical companies' spending on R&D had been criticized for being well below international averages: in the range of 3.5% to 4.5% of sales in Canada versus 6% to 7.2% in the United States from 1967 to 1982 (Canada 1963, 1985). While some research suggests otherwise (Gorecki 1981; Gorecki and Henderson 1981), the relatively low level of R&D investment in Canada may have stemmed, in part, from the fact that Canada had a compulsory licensing provision of the *Patent Act* that, since 1969, permitted any firm to license the technology for a patented drug subject to a fixed 4% royalty payment made to the patent holder. Under the policy, the patentee could not block the licensing of patents – hence, they were “compulsory.” Compulsory licensing for pharmaceuticals was designed to encourage price competition for patented and non-patented products alike, motivated by a belief that drug manufacturers had greater market power than producers of other types of patent-protected products because of the unique complexities of the pharmaceutical market (Canada 1963, 1985).

The compulsory licensing provision of the Canadian *Patent Act* was gradually eliminated at the request of industry in negotiating processes tied to the Canada–US Free Trade Agreement (negotiated 1985–1988) and the North American Free Trade Agreement (negotiated 1990–1992) (Lexchin 1993). Bill C-22, introduced in 1987, gave patent holders a guaranteed period of market exclusivity of 10 years before generics could receive a compulsory license; Bill C-91, introduced in 1993, eliminated compulsory licensing altogether. In exchange for these changes in the *Patent Act*, manufacturers of patented medicines promised to raise R&D to more than 10% of sales by 1996 (Pazderka 1999). The government created the Patented Medicine Prices Review Board (PMPRB) in 1987 – as a part of Bill C-22 – to monitor prices and R&D activities. The PMPRB was to prevent price gouging in the absence of generic competition and to report on whether patenting pharmaceutical firms upped R&D to 10% of sales by 1996 as promised.

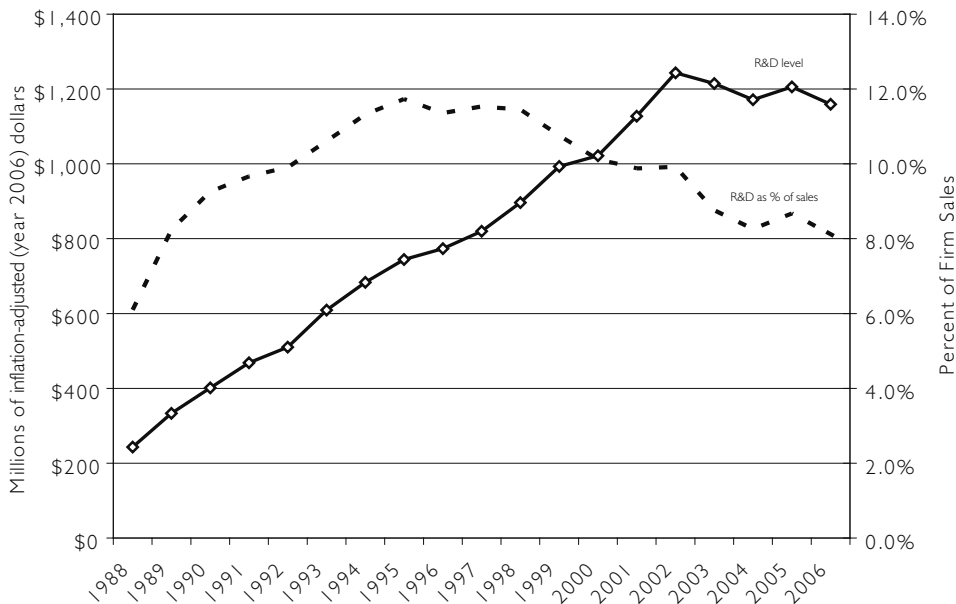
For the period of 1988 to 2006, Figure 1 reports PMPRB statistics regarding total Canadian R&D by patent-holding firms as a percentage of firm sales and in inflation-adjusted expenditures (year 2006 dollars). These official PMPRB data are based on industry self-report and reflect the (unaudited) amounts that firms report they spend on R&D by location and type of activity. While firms may have incentives to overstate R&D amounts – in order to appear to have lived up to promised levels of R&D (Kalant and Shrier 2006) – the impact of such incentives should not affect this analysis of BC PharmaCare's policy impacts. For example, in their analysis of the national impact of changes in drug patent policy, Grootendorst and Di Matteo (2007) found comparable results using the PMPRB data versus data from Statistics Canada. We



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used PMPRB data because publicly available Statistics Canada data on pharmaceutical R&D are not available at a regional level. PMPRB reports R&D expenditures by companies marketing patented drugs that belong to the brand-name industry association (Rx&D) and by all pharmaceutical companies marketing patented drugs. For this analysis we used the latter set of data.

**FIGURE 1.** Total R&D expenditure by patent-holding pharmaceutical companies in Canada in inflation-adjusted (year 2006) dollars and as percentage of firm sales, 1988 to 2006

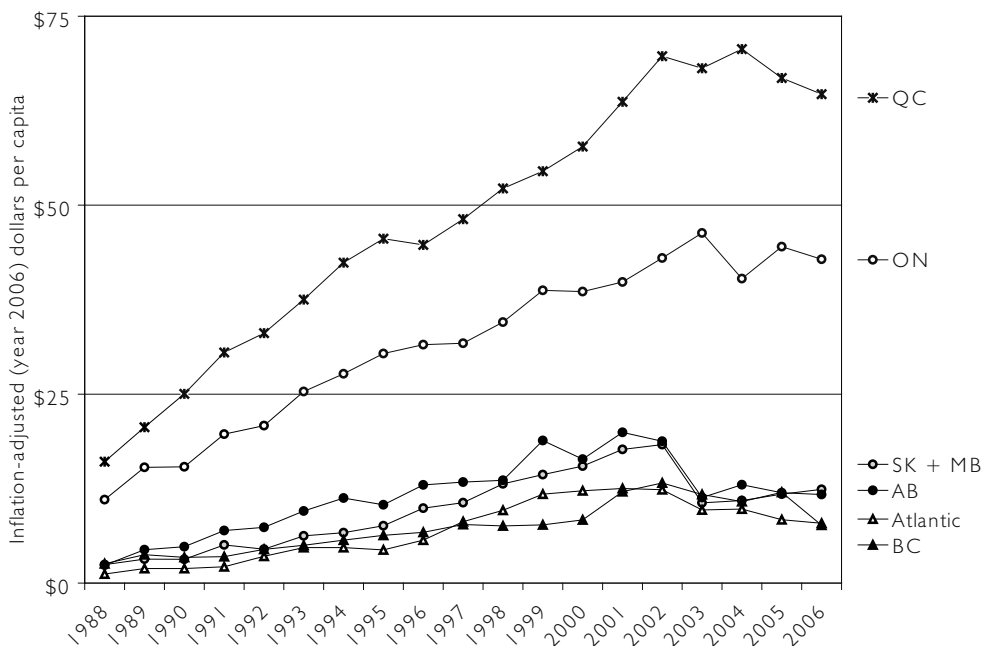


Source: Authors' calculations based on data from the Patented Medicine Prices Review Board, Ottawa.

The data illustrated in Figure 1 show that industry met its promise to spend 10% of revenue on R&D in the 1990s, but thereafter let performance on this measure deteriorate to below promised levels (for further discussion of this trend, see the analysis of Kalant and Shrier 2006). After adjusting for inflation, industry-financed R&D expenditure grew steadily between 1988 and 2002, from \$243 million (in year 2006 dollars) in 1988 to \$1.24 billion in 2002. Spending has since fallen in inflation-adjusted terms to \$1.16 billion in 2006. Taking into account trends in pharmaceutical R&D from before patent changes, as well as more general trends in Canadian R&D (using the automotive sector as a control for this), Grootendorst and Di Matteo (2007) found that the total increase in Canadian pharmaceutical R&D following the change in patents amounted to approximately \$4.4 billion over 15 years, or \$293 million per year.

Figure 2 illustrates regional, inflation-adjusted (year 2006) R&D expenditure per capita by patent-holding pharmaceutical companies from 1988 to 2006. Consistent with Statistics Canada reporting of R&D procedures, we grouped the data reported for Saskatchewan and Manitoba together, and also grouped data for the Atlantic provinces. This approach reduces spurious volatility in measures for regions with small populations because the initiation or completion of a single scientific study could significantly skew data for provinces with populations of a million or less.

**FIGURE 2.** R&D expenditure by patent-holding pharmaceutical companies by province in inflation-adjusted (year 2006) dollars per capita, 1988 to 2006



Source: Authors' calculations based on data from the Patented Medicine Prices Review Board, Ottawa.

After adjusting for inflation and population, annual R&D investment by patent-holding firms varied significantly across provinces. Consistent throughout the period 1988 to 2006, per capita investments in R&D activities by patent-holding firms in Quebec and Ontario were respectively more than five and three times as great as were investments in all the rest of Canada together. Expenditure in these two provinces grew steadily through 2002 and then levelled off, driving Canadian trends overall. Expenditure per capita on R&D outside Quebec and Ontario was relatively volatile over the period: spending grew quickly in the prairies through 2002 and then fell back in line with other provinces in 2003 and onward. With the decline in pharmaceutical

R&D activities in the prairie provinces from 2003 onward, there are now “two Canadas” with respect to pharmaceutical R&D: Ontario and Quebec, with moderately high levels of R&D investment per capita, and the rest of Canada, with very little pharmaceutical R&D. Figure 2 also highlights the fact that British Columbia (along with Atlantic Canada) has long had the distinction of having among the lowest levels of investment in R&D activities by patent-holding pharmaceutical companies in Canada.

## Impact of Evidence-Based Drug Coverage Policies on R&D in BC

### Data

PMPRB data on pharmaceutical company R&D expenditures provide information necessary to determine whether British Columbia’s evidence-based drug coverage policies, and in particular its reference pricing policy, had a significant effect on local R&D investment. If BC PharmaCare’s policies affected local R&D investments, this impact should be observed in measurable changes in BC-based R&D by pharmaceutical companies; these changes should be observable in absolute terms, in comparison to the rest of Canada, or both.

In addition to these data on pharmaceutical R&D by patent-holding firms (those that are required to file data to the PMPRB), we also collected information on non-pharmaceutical R&D by province, provincial incomes and biotechnology R&D. Because publicly available Statistics Canada data on regional R&D are not sector-specific, we took regional Statistics Canada data on total business expenditure on R&D in all sectors and subtracted regional PMPRB data on pharmaceutical R&D. The result is an estimate of non-pharmaceutical R&D by province. We also collected Statistics Canada data on provincial gross domestic product (GDP) by province; these data were deflated using the GDP price deflator to give inflation-adjusted (year 2006 prices) estimates of total income in each province.

Finally, we used data from Statistics Canada’s *Biotechnology Use and Development Survey* to provide some information about R&D investment by biotechnology firms in British Columbia and other provinces. While Statistics Canada’s data do not break down biotechnology R&D by province and nature of research, biotech R&D related to human health accounted for 87% of the total \$1.7 billion in national biotech R&D during 2005. As such, levels and trends in total provincial biotech R&D can serve as a reasonable proxy for biotech R&D related to human health.

## Methods

We searched for evidence of an impact of PharmaCare policy in BC-based R&D by pharmaceutical companies in two ways. First, we searched for changes in inflation-adjusted pharmaceutical R&D expenditure per capita in British Columbia, controlling for pre-policy time trends. Second, just as researchers use other economic sectors to control for general trends in R&D when studying total pharmaceutical sector R&D (Grootendorst and Di Matteo 2007), we used trends in pharmaceutical R&D in the rest of Canada to control for factors that might be affecting BC-based R&D in ways other than the specific PharmaCare policies studied here. To do this, we looked for changes in the ratio of expenditure per capita in British Columbia over expenditure per capita in the rest of Canada, controlling for pre-policy time trends in that ratio.

We performed a time series analysis (using SAS for Windows v.9) to test for changes in trends or levels of BC-based pharmaceutical R&D. The models computed were linear ordinary least squares regressions with co-variance matrices adjusted for autocorrelation. Our models took the following form:

$$(1) BCR\&D_t = \alpha + \beta \times trend_t + \delta \times policylevel_t + \gamma \times policytrend_t + \varepsilon$$

and

$$(2) [BCR\&D_t / ROCR\&D_t] = \alpha + \beta \times trend_t + \delta \times policylevel_t + \gamma \times policytrend_t + \varepsilon$$

where  $BCR\&D_t$  and  $ROCR\&D_t$  are, respectively, inflation-adjusted per capita R&D in British Columbia and in the rest of Canada during year  $t$ ;  $trend_t$  is a count of years since 1988;  $policylevel_t$  is a dummy variable to account for one-time changes in the absolute level of R&D after the policy (e.g., 1995); and  $policytrend_t$  is a count of years since the policy to detect changes in the rate at which R&D grew after the policy. Evidence of policy impact will be found in the terms  $\delta$  and  $\gamma$ .

In separate regressions (owing to lack of statistical degrees of freedom), we tested for policy impacts following 1995 (the year reference pricing was initiated for three drug classes) and following 1997 (the year the program was expanded to two further classes). Finally, after visual inspection of the data, we tested for temporary changes in BC-based R&D during the periods of 1998 to 2000 and 2001 to 2003 because BC-based R&D in those periods appeared to be below and above trends, respectively. There was an as-yet-unexplained 36% decrease in pharmaceutical company spending on BC-based R&D in 2006. Findings of our statistical analysis were not affected by the exclusion of that data point.

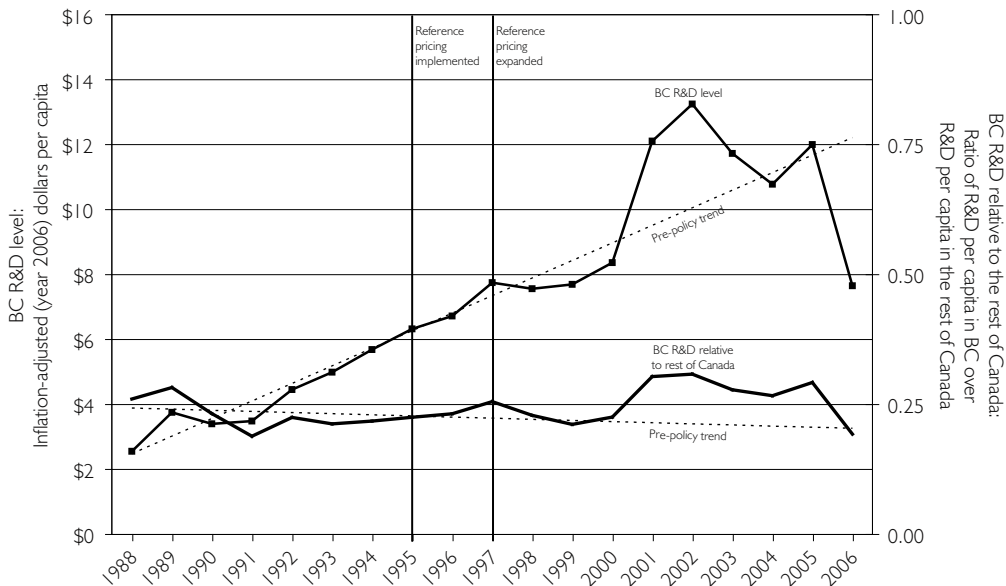
Following the analysis of PMPRB data on R&D by patent-holding pharmaceutical companies, we also explored trends in total non-pharmaceutical R&D, income and biotechnology R&D by province. Data were graphed and summarized using summary statistics.

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Results

Figure 3 illustrates pharmaceutical R&D expenditure for British Columbia in inflation-adjusted (year 2006) dollars per capita and as a ratio over expenditure per capita in the rest of Canada. The figure also illustrates forecast data based on a best-fitting time series regression model using the pre-policy data spanning 1988 to 1997. Forecasts from 1988 to 1995 are similar but suggest a more modest policy impact because the increase in BC R&D from 1995 to 1997 was more rapid than pre-policy trends. We chose to illustrate the 1988 to 1997 model in order to bias against understating the policy impact.

FIGURE 3. Per capita R&D expenditure in British Columbia by patent-holding pharmaceutical companies in inflation-adjusted (year 2006) dollars and as a ratio of per capita expenditure in the rest of Canada (ROC), 1988 to 2006



Source: Authors' calculations based on data from the Patented Medicine Prices Review Board, Ottawa.

Table 1 lists the regression results for the models specified above. There were no statistically significant changes in either the level or the trend of BC-based pharmaceutical R&D in absolute terms or relative to the rest of Canada following the implementation (1995) or expansion (1997) of reference pricing. However, per capita investment in British Columbia plateaued from 1998 to 2000. While it is not statistically significant ( $p=.51$  for per capita levels,  $p=.17$  for ratios relative to the rest of Canada), if the decline in BC-based R&D from 1998 to 2000 were attributable to BC

PharmaCare’s policies, the potential R&D lost (in comparison to trend) would be valued at \$6.5 million (year 2006 dollars), or roughly \$2 million per year for three years. From 2001 to 2003, BC-based R&D increased to statistically significant levels above trends ( $p < .01$  for per capita levels and for ratios relative to the rest of Canada). The increase in BC-based R&D investment by patent-holding drug companies from 2001 to 2003 would be valued as a windfall (in comparison to trend) of \$28.5 million (year 2006 dollars), or about \$9 million per year for three years.

TABLE 1. Regression results

Variable / Model	Intercept	Time Trend	Change in Level	Change in Trend	r-square
<b>1995 changes</b>					
BCR&D	2.408	0.428	1.194		.8
<i>p</i> -value	<.01	<.01	.41		
BCR&D/ROCR&D	0.231	-0.0001	0.024		.11
<i>p</i> -value	<.01	.97	.46		
BCR&D	1.764	0.608		-0.134	.79
<i>p</i> -value	.14	<.01		.64	
BCR&D/ROCR&D	0.252	-0.003		0.008	.17
<i>p</i> -value	<.01	.4		.19	
BCR&D	2.097	0.497	1.11	-0.095	.8
<i>p</i> -value	.11	.06	.74	.46	
BCR&D/ROCR&D	0.262	-0.007	0.032	0.009	.22
<i>p</i> -value	<.01	.2	.31	.15	
<b>1997 changes</b>					
BCR&D	2.511	0.437	1.055		.8
<i>p</i> -value	<.01	<.01	.47		
BCR&D/ROCR&D	0.234	-0.0001	0.024		.11
<i>p</i> -value	<.01	.95	.46		
BCR&D	1.644	0.622		-0.202	.8
<i>p</i> -value	.12	0.01		.45	

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TABLE 1. Continued.

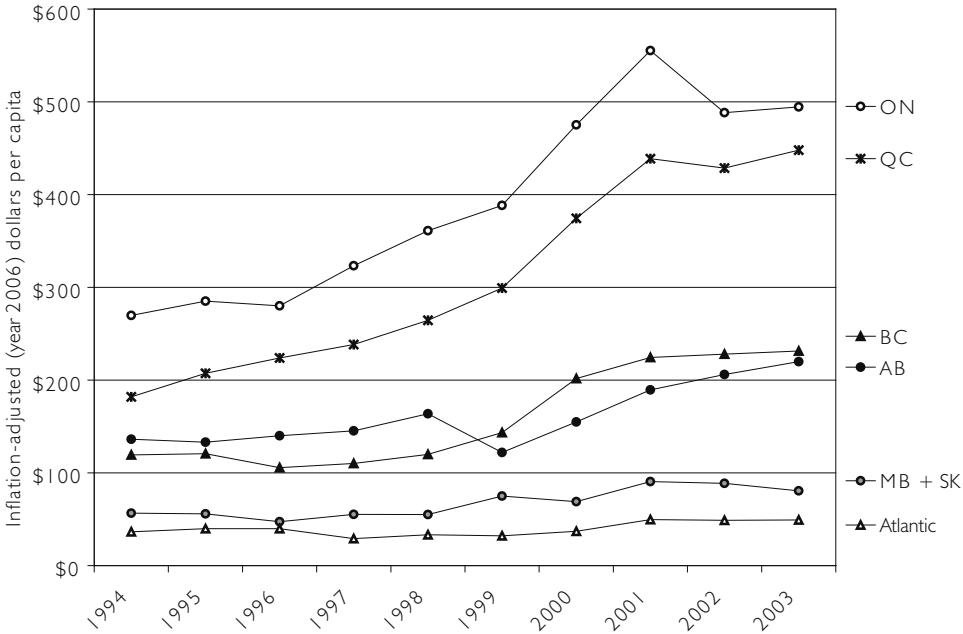
Variable / Model	Intercept	Time Trend	Change in Level	Change in Trend	r-square
<b>1997 changes</b>					
BCR&D/ROCR&D	0.24	-0.0009		0.005	.12
<i>p</i> -value	<.01	.78		.38	
BCR&D	1.942	0.54	1.301	-0.24	.8
<i>p</i> -value	.09	<.01	.39	.37	
BCR&D/ROCR&D	0.245	-0.002	0.02	0.004	.14
<i>p</i> -value	<.01	.59	.56	.45	

Relative to the rest of Canada, pharmaceutical company R&D in British Columbia was low and on a slightly – though not statistically significant – downward trend through the pre-policy era (1988 to either 1995 or 1997). During the pre-policy period, per capita spending on R&D in the province was approximately 75% to 80% lower than per capita spending on R&D in the rest of Canada. The relative size of BC-based R&D investment trended slightly – though not statistically significantly – upward through the post-policy period. From 2001 to 2005, per capita pharmaceutical R&D was approximately 70% lower in British Columbia than in the rest of Canada.

### BC R&D in pharmaceutical and non-pharmaceutical sectors

Another way to test for an R&D impact of BC PharmaCare's policies is to compare BC-based private expenditure on R&D in the pharmaceutical sector against that in other sectors over the relevant period. Figure 4 illustrates our estimates of inflation-adjusted (year 2006) dollars per capita private sector investment in non-pharmaceutical R&D in each region for the period 1994 to 2003 (the period for which regional Statistics Canada data are available). Again, Ontario and Quebec dominate non-pharmaceutical business R&D investment, though not nearly to the extent that those provinces dominate pharmaceutical sector R&D investment. Non-pharmaceutical R&D investment in British Columbia was third highest in Canada from 1999 to 2003 as a result of significant growth between 1998 and 2001.

FIGURE 4. Business expenditure on non-pharmaceutical R&D by province in inflation-adjusted (year 2006) dollars per capita, 1994 to 2003



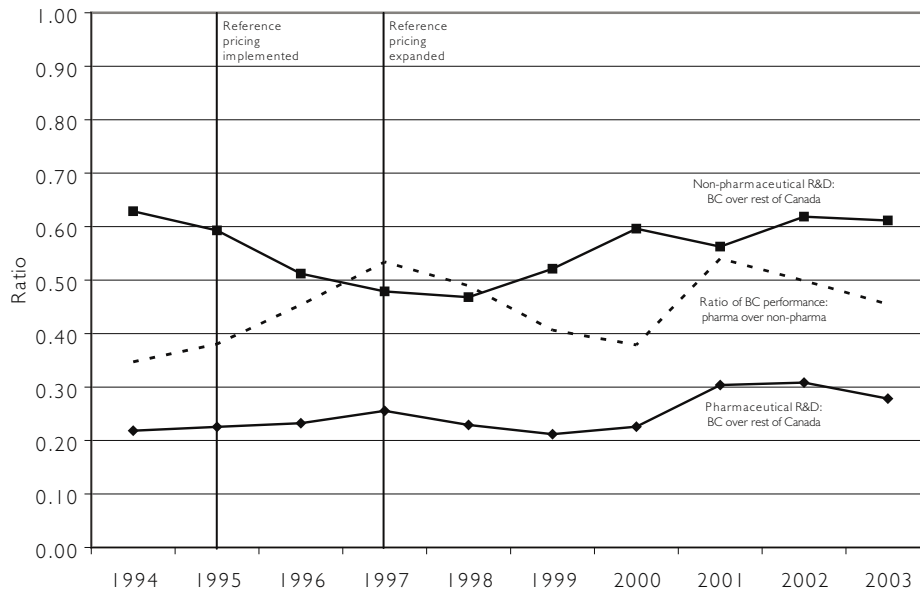
Source: Authors' calculations based on data from Statistics Canada and the Patented Medicine Prices Review Board, Ottawa.

Figure 5 illustrates per capita private sector investment in non-pharmaceutical R&D and pharmaceutical R&D in British Columbia relative to the rest of Canada for the period 1994 to 2003. British Columbia's performance in non-pharmaceutical R&D per capita – which ranged from 40% to 60% of the per capita levels in the rest of Canada – is superior to pharmaceutical R&D in all years for which data are available. However, for our purposes what matters is how pharmaceutical and non-pharmaceutical R&D fluctuate over time, and whether there is evidence of a policy-related decline in British Columbia's performance in pharmaceutical R&D relative to its performance in non-pharmaceutical R&D (both relative to the rest of Canada).



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**FIGURE 5.** Private expenditure on pharmaceutical and non-pharmaceutical R&D in British Columbia relative to the rest of Canada, 1994 to 2003



Source: Authors' calculations based on data from Statistics Canada and the Patented Medicine Prices Review Board, Ottawa.

There was little overall trend in British Columbia's performance (relative to the rest of Canada) in non-pharmaceutical R&D. The province's non-pharmaceutical R&D expenditures decreased compared to the rest of Canada from 1994 through 1998 and then increased through 2003, finishing just slightly below the performance seen in 1994. As reported above, British Columbia's performance (relative to the rest of Canada) in pharmaceutical R&D showed a marginal upward trend over the period, interrupted by a slight decline between 1997 and 1999.

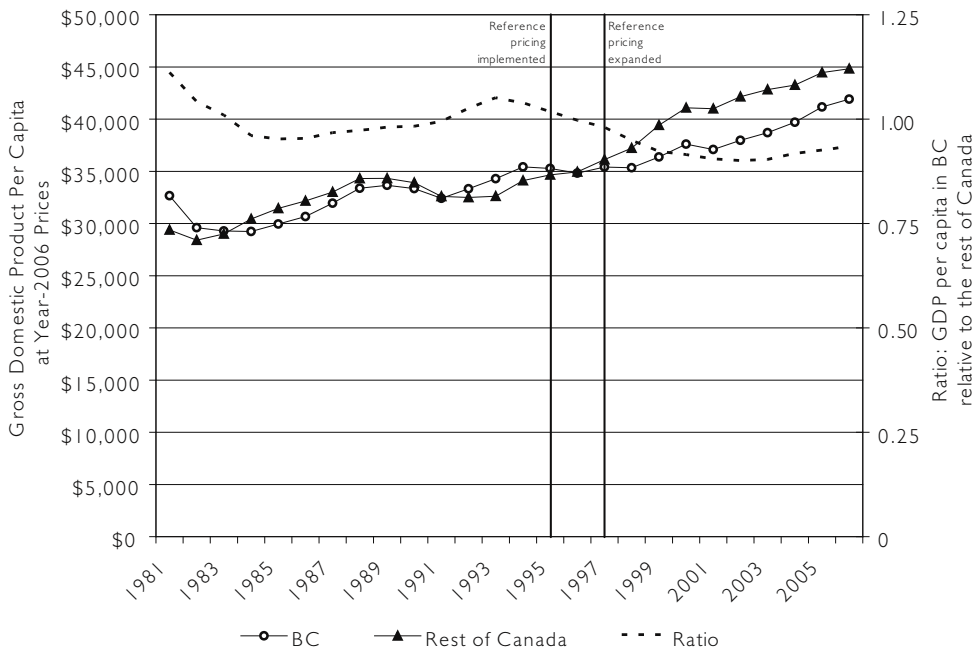
Overall, British Columbia's performance in terms of pharmaceutical R&D relative to non-pharmaceutical R&D (the dashed line in Figure 5) shows variation on a slight upward trend: that is, relative to the rest of Canada, the province's levels of private expenditure on pharmaceutical R&D outperformed its levels of private expenditure on non-pharmaceutical R&D over the entire period. There was a notable decline in performance in pharmaceutical versus non-pharmaceutical R&D from 1998 to 2000. However, had British Columbia's performance in non-pharmaceutical R&D not fallen relative to the rest of Canada during the implementation of reference pricing – that is, had the upper line in Figure 5 stayed flat at approximately 60% from 1994 to 2000 – there would have been steady improvement in pharmaceutical R&D relative to non-pharmaceutical R&D over the entire period. Income-related factors (explored below) may have driven the decline and subsequent return in British Columbia's performance on non-pharmaceutical R&D from 1994 to 2000.

## Other Possible Influences on Pharmaceutical R&D

There are two further influences on pharmaceutical R&D that might have affected British Columbia's performance over the period of study: (1) income growth in the province and the rest of Canada, and (2) changes in the trend in pharmaceutical R&D.

It is possible that changes in income per capita would imply that R&D in British Columbia might have been even higher than observed above. If this were true, an increase in BC incomes (such that one might have expected greater economic activity in the province) would have had to occur exactly when the BC PharmaCare program changed its coverage policies, and the increase would have had to occur relative to the rest of Canada (given the evidence above that British Columbia's performance vis-à-vis the rest of Canada was unchanged). Statistics Canada data on inflation-adjusted (year 2006 prices) provincial GDP per capita do not support this hypothesis (see Figure 6). Inflation-adjusted GDP per capita fell in British Columbia and the rest of Canada during the early 1980s and late 1980s. Following an early 1990s recovery from losses of the late 1980s, inflation-adjusted GDP per capita in British Columbia was stagnant from 1994 to 1998. It thereafter grew relatively steadily through 2006. Inflation-adjusted GDP per capita in the rest of Canada showed a steadier recovery from the losses of the late 1980s, growing relatively unabated from 1993 through 2006. As a result, the ratio of GDP per capita in British Columbia relative to the rest of Canada fell slightly from 1993 through 2003.

FIGURE 6. Inflation-adjusted (year 2006 prices) GDP per capita in British Columbia and the rest of Canada



Source: Authors' calculations based on data from Statistics Canada.

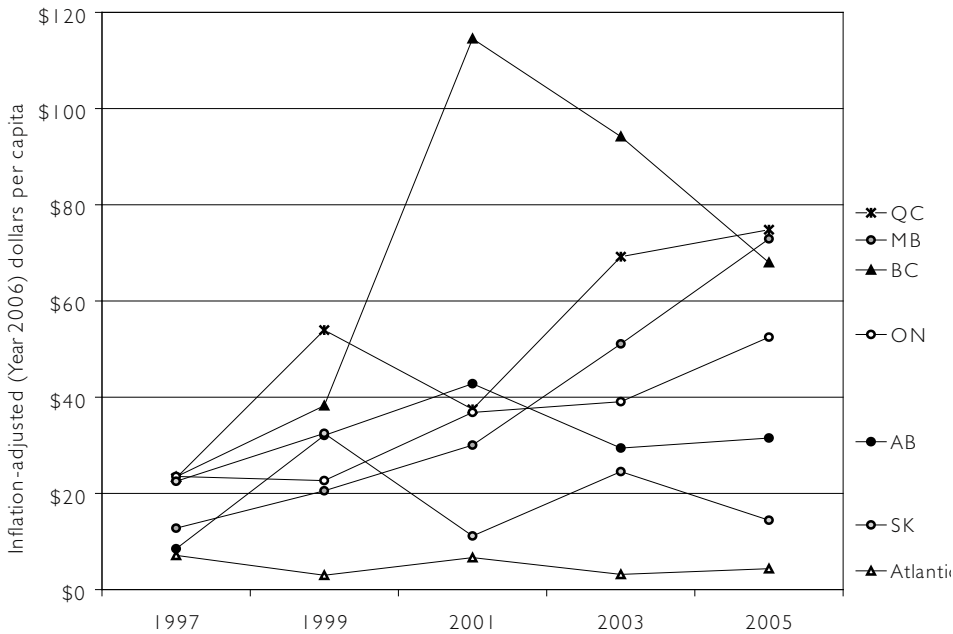
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If regional income influences regional R&D then, holding other things equal, BC's R&D performance should have showed a levelling trend from 1994 to 2001 and a decline relative to the rest of Canada over the same period. The results presented above indicate that BC-based pharmaceutical R&D did not decline following BC PharmaCare's evidence-based coverage policies, despite the potentially negative effect of GDP performance in the province. This finding provides further evidence for rejection of the hypothesis that BC PharmaCare's policy had a negative impact on BC-based pharmaceutical R&D.

A final potential influence on pharmaceutical R&D in British Columbia and elsewhere is the pharmaceutical industry's trend towards the development of new drugs by niche firms, with clinical trials the major research activity of larger companies – particularly in countries like Canada (Kondro 2006). This possibility would suggest that one should not have expected significant growth in BC-based pharmaceutical R&D over the period being analyzed here. While we found that pharmaceutical companies continued to increase their R&D activities in the province following BC PharmaCare's evidence-based coverage policies, industry trends towards product development by niche firms might lead some to suggest that BC PharmaCare's policies might reduce BC-based R&D by smaller firms.

Statistics Canada's *Biotechnology Use and Development Survey* data provide some information about R&D investment by biotechnology firms in British Columbia and other provinces. Figure 7 illustrates inflation-adjusted (year 2006) total biotech R&D per capita by province in 1997, 1999, 2001, 2003 and 2005 (years for which data are available). These are all post-policy years for the purpose of our analysis. However, the key finding in Figure 7 is that British Columbia's performance on biotech R&D was strong – in levels, trends and relative to other provinces – following the implementation and expansion of reference pricing in the province.

FIGURE 7. Biotechnology R&D expenditure by innovative biotechnology firms in inflation-adjusted (year 2006) dollars per capita, 1997 to 2005.



Source: Authors' calculations based on data from Statistics Canada.

## Discussion

In light of the statistical results concerning pharmaceutical R&D, non-pharmaceutical R&D, incomes, and biotech R&D reported above, we conclude that available data do not provide evidence that BC PharmaCare's policies had a significant, negative impact on BC-based pharmaceutical R&D. Of course, policy analysis is often challenging because of the difficulty of finding valid counterfactuals against which to compare policy experience. In this case, it is hard to know with certainty what R&D investment would have been without reference pricing policy. Evidence suggests that reference pricing in British Columbia did not cause any significant changes in R&D expenditures in the province by the pharmaceutical industry, either in absolute terms or compared with the rest of Canada. BC-based pharmaceutical R&D continued to grow following the implementation of evidence-based drug coverage policies – indeed, it did so slightly more quickly following these policies than preceding them. Industry will, however, continue to claim the policy created a hostile environment that decreased investment potential. Pharmaceutical companies have long cited local market conditions as influences on R&D investment decisions (Taggart 1991; OECD 2006). Taggart (1991) describes this as surprising “because there seems to be no *prima facie*

reasoning that would immediately lead to this conclusion”; in other words, it defies basic economic logic.

How so? Pharmaceutical companies are businesses before anything else. As such, they make investment decisions based on expected costs and benefits. For example, literature on location of R&D from this sector and others states that, on the cost side of R&D investments, firms will consider such factors as the effect of tax breaks on the cost-to-firm of local R&D spending (Taggart 1991; Cornet and Rensman 2001; Davis and Meyer 2004; OECD 2006; Pazderka 2007). It is notable that Canada’s R&D tax breaks are among the most generous in the world (OECD 2005). However, as evidenced by Canada’s relatively poor R&D performance (Guellec and de la Potterie 2001; Harris 2005; Conference Board of Canada 2007; Howitt 2007), tax breaks are not sufficient to make significant local R&D investment of value to firms.

An increasing amount of research suggests that the most important consideration in R&D investment decisions – even more so than tax breaks – is the availability, accessibility and quality of local technical infrastructure and scientific capacity (Jaffe 1989; Cockburn and Henderson 1996; Mansfield and Lee 1996; Porter 1998, 2000; Kuemmerle 1999; Davis and Meyer 2004). These factors are critical insofar as they relate to the research productivity and therefore expected return from a firm’s R&D investments. Across many studies, the availability and cost of high-quality labour ranks as a crucial determinant of R&D location (Taggart 1991; Cornet and Rensman 2001; OECD 2006); also important is the location of productive universities and related laboratories (Jaffe 1989; Cockburn and Henderson 1996; Mansfield and Lee 1996; Kuemmerle 1999; Davis and Meyer 2004). Indeed, through the accumulation of past investment decisions, and the existing stock of talented researchers, there is a degree of path dependence in R&D location decisions (Arthur 1989, 1990; Krugman 1991; Taggart 1991; Porter 1998, 2000). If a critical mass of scientific activity builds up as a function of public and private investment, it can have a gravitational effect that draws further investment into the area as firms aim to capitalize on the many synergies generated by a vibrant, concentrated and, ideally, well-connected local scientific community (Porter 1998, 2000). As corporate and scientific investments grow in a given region, so grows the reward needed to lure firms to invest in distant projects for which performance monitoring and information transfer will be more difficult and more costly.

Thus, firms may never have intended to cut R&D in British Columbia or to increase R&D investment in the province more quickly than they actually did over the past decade. One might not have expected further *increases* in BC R&D because of the historical concentrations of traditional pharmaceutical investments elsewhere in the world (and elsewhere in Canada). Indeed, for as long as comparable data have been available, British Columbia has been a relatively low-performing province in terms of private expenditure on R&D in the pharmaceutical sector (fluctuating from 20% to

30% of R&D per capita in the rest of Canada) and, to a lesser extent, in other sectors (fluctuating from 47% to 63% of R&D per capita in the rest of Canada).

Despite the business economics of R&D investments, firms may find that the rhetoric of punishment serves to build opposition to evidence-based drug coverage policies in other jurisdictions. Firms may find it rational therefore to occasionally “defy basic economic logic” in the short term through the use of R&D investments as rewards or punishments for government actions. However, this too is a business decision – and a risky one, at that.

Withdrawing R&D investments that would otherwise be profitable will always represent an economic loss in the short run. Whether withdrawing otherwise profitable R&D investments will generate long-term returns depends on whether punishing by example creates benefits that outweigh lost short-term profit opportunities. Benefits of punishment would arise from changes in policies in the local jurisdiction and elsewhere. The costs of punishing arise from forgone opportunities to employ local scientific expertise and to take advantage of local tax breaks. For threats of punishment to be credible, pharmaceutical companies must be united in their local “boycott” and must sustain their support for it for sufficiently long to make it clear to local and foreign decision-makers that firms will punish themselves (by forgoing otherwise profitable local scientific endeavours) in order to punish governments who employ certain drug coverage policies.

If a region with an evidence-based coverage policy, such as reference pricing, also provides strong scientific opportunities and competitive tax incentives, any industry coalition in protest of policies will be unstable. Some firms will find it in their individual self-interest to “cheat” on their competitors by investing in local R&D. Evaluating the credibility of industry’s threats to withdraw R&D investments because of coverage policy, the Australian Government Productivity Commission concluded that “it is not clear that this type of bargaining power is significant, particularly since pharmaceutical firms do not coordinate their bargaining. A threat by a single firm may be hollow if other firms continue to undertake activity” (Productivity Commission 2003).

## Conclusion

Manufacturers claim that “drug policy and economic development are indissociable” (Williams 2006). In response to the possible introduction of reference pricing in Ontario, Rx&D suggested “we must be careful that Ontario remains competitive in the world and does not create policies that inhibit Ontario’s ability to attract R&D investments” (Rx&D 2006). During discussions of possible drug policy changes in Quebec, Rx&D argued that “to ensure the strength of the industry, we believe there must be total synergy between drug policy and Quebec’s economic policy, which also relies on a strong, innovative pharmaceutical industry generating high quality jobs”

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(Williams 2006). The message is clear: we will punish provinces that adopt reference-based pricing by taking away investment – and the resulting jobs and indirect economic benefits.

Despite industry claims, we found no evidence to suggest that pharmaceutical manufacturers pulled R&D investment from British Columbia following BC PharmaCare's implementation of evidence-based policies, and reference pricing in particular, in the mid-1990s. The reason: threats of punishment do not stand up against business fundamentals. Industry will invest in local R&D based on the costs and benefits incurred from that scientific investment. Such factors are totally independent of local coverage policy except to the extent that firms try to associate them through the rhetoric of rewards and punishment. Even in the case of a policy as harshly opposed as reference pricing in British Columbia, the threats are not credible because firms will maintain their R&D investments as long as R&D fundamentals are unchanged.

Government policies most likely to affect R&D investment are those concerning the availability and cost of specialized researchers and facilities and proximity of academic research facilities. Prudent public policy would therefore manage pharmaceutical expenditures using evidence-based policies – which evidence from British Columbia shows can achieve cost-control and patient health goals (Grootendorst and Holbrook 1999; Hazlet and Blough 2002; Morfitt et al. 2002; Schneeweiss, Soumerai et al. 2002; Schneeweiss, Walker et al. 2002; Schneeweiss et al. 2003, 2004; Morgan et al. 2004) – and to pursue scientific and economic development goals through direct and strategic government investment in local scientific capacity. Provinces like British Columbia would be well advised to consider strategic support of scientific research in other areas, such as biotechnology, rather than competing (at significant cost to taxpayers) to overcome the pull of historical concentration of pharmaceutical investments in other, distant locations.

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#### ACKNOWLEDGMENTS

This project was supported by the Centre for Health Services and Policy Research (CHSPR) at the University of British Columbia. CHSPR is supported in part by the BC Ministry of Health and a Research Unit Award from the Michael Smith Foundation for Health Research (MSFHR). Steve Morgan is supported by a New Investigator award from the Canadian Institutes of Health Research (CIHR) and Scholar Award from MSFHR. The views presented here are solely those of the authors and not necessarily those of CHSPR, the BC Ministry of Health, CIHR or MSFHR.

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