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BENEFITS OF PHARMACEUTICAL INNOVATION: THE CASE OF SIMVASTATIN IN CANADA

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Background: The benefits of pharmaceutical innovations are widely diffused; they accrue to the healthcare providers, patients, employers, and manufacturers. We estimate the societal monetary benefits of simvastatin in Canada and its distribution among different beneficiaries overtime.
Methods: Monetary benefits to developing and generic manufacturers were estimated by calculating public and private revenues minus the development costs of simvastatin and the contribution toward further research and development. We used a dynamic Markov model to estimate monetary benefits to healthcare and employment sectors in terms of cost avoidance associated with prevented cardiovascular events, including stroke and myocardial infarction, and lost productivity due to disability and premature death in working population.
Results: Cumulative monetary benefits of simvastatin from 1990 to 2009 were $4.8 billion (2010 CA$), of which developing and generic manufacturers, and healthcare and employment sectors accounted for 32 percent, 27 percent, 32 percent, and 9 percent, respectively. The yearly trend showed that after the patent expired in 2002 the generic manufacturers became dominant in the market. Benefits for the healthcare sector started to decrease from 2003 corresponding to the decreasing population taking simvastatin during the same time period. Sensitivity analysis showed the higher the compliance or the efficacy, the larger the benefits to healthcare and employment sectors, while monetary benefits for manufacturers were unchanged.
Conclusions: Societal monetary benefits of simvastatin are significant and the distributions of the benefits have changed overtime. Patent, compliance, and efficacy play a vital role in the estimation of the benefits. Analysis of all beneficiaries separately overtime is important when assessing the value of pharmaceutical innovation.

Keywords: Societal monetary benefits, Pharmaceutical innovation, Simvastatin, Canada

The pharmaceutical industry is under continual scrutiny by shareholders to generate sales and by public and private payers to contain prices and expenditures of pharmaceutical products (25–27). Pharmaceutical products, however, are inextricably linked with achieving the benefits of improved health outcomes for patients receiving therapy (9). Consequently, policy makers face the increasingly difficult challenge of weighing budgetary constraints against rising pharmaceutical expenditures (7) coupled with the increasing public demand for access to effective pharmacotherapies (14).

The market access requirements from regulatory and reimbursement authorities are concentrated mainly on safety, effectiveness, cost-effectiveness, and budgetary impact of new drugs (5). What is missing from the discussion around pharmaceutical reimbursement policies is the analysis of the benefits of stakeholders overtime showing how much and when different stakeholders benefit from innovative drugs.

Simvastatin is a good example of a drug innovation that was shown to be effective and cost-effective (16). Cost-effectiveness models provide information to decision makers from the value for money perspective. However, it does not provide a good estimate of monetary benefits for different stakeholders at a country level considering all the country specific market and healthcare factors, and considering the benefits created overtime. An example of country level "value of innovation" analysis is the 2011 study by Lindgren and Jonsson (18) that estimated societal surplus of statins in Sweden between 1987 and 2028. Societal surplus was defined as producer and consumer surplus where producer surplus was 80 percent and 20 percent of retail revenues during on-patent and after patent periods, respectively. Consumer surplus was estimated using three methods: monetary value for each quality-adjusted life-year (€75,000), value for life-year gained (€70,000), and value of a statistically saved life (€1.1 million) produced by the drugs in Sweden subtracted from the retail price of the drugs. The study showed that the consumer benefits were much higher than producer' benefits even during the patent period. After the patent period, approximately 99 percent of the surplus was created by the reduced mortality and morbidity (18). Although the study succeeded to estimate value of innovation overtime for drug producers and patients, it did not separate the values created by the developing and generic producer and did not compare them with the value that is created by savings in the healthcare and employment sectors due to reduction in service uses and work productivity losses.

The aim of this study is to estimate the Canadian monetary benefits overtime for simvastatin, i.e., the first statin in the market, among four primary beneficiaries: the drug developing manufacturer, the generic manufacturers, the healthcare sector, and the employment sector (i.e., lost productivity).

METHODS

In this study, monetary benefits were calculated for simvastatin, which is a hypolipidemic drug used to control hypercholesterolemia. Simvastatin was chosen because it was the first statin, had good evidence of its long-term effectiveness, and the first to go out of patent, which could allow us to show a clear trend of the benefits overtime. The target population consisted of individuals with hypercholesterolemia in Canada who were prescribed simvastatin. Time horizon for the analysis was from 1990 to 2009, representing the time from market entry to the most recent year of data available. The monetary benefits in this study focused on four beneficiaries (or components), including benefits to developing and generic manufacturers, and benefits to healthcare and employment sectors. We excluded intangible benefits to the patients, such as benefits due to improvement in health-related quality of life.

Benefits to Developing and Generic Manufacturers

Monetary benefits to developing and generic manufacturers were estimated separately by calculating public and private revenues minus the contribution toward further research and development (R&D) (estimated at 8 percent of annual revenues) and minus the original development costs of bringing the product to market (one time). The revenues were obtained from the Information Management System database, which provides the actual payment activities of public and private drug plans in Canada (www.imsbrogan.com). The Canadian development costs of simvastatin were estimated at approximately $48 million, which was equal to 3 percent of the average global development costs (this was assumed to be the same as Canadian share of the global revenues) for a cardiovascular drug ($1.6 billion) (1). We annually deducted $2.4 million from the annual revenues of the developing manufacturer in 20 years to get the total deduction of $48 million.

Benefits to Healthcare Sector and Employment Sector

Monetary benefits to the healthcare sector were defined as the cost avoidance of prevented adverse cardiovascular events; that is, the costs due to reduced health service usage resulting from the better control of hypercholesterolemia associated with simvastatin. These adverse events included both fatal and nonfatal stroke and acute myocardial infarction (AMI), while the reduction in health service usage included hospital days and physician visits (general practitioners and specialists).

Monetary benefits to the employment sector were defined as the reduction in lost productivity from premature death or disability following a cardiovascular event in the working population. Monetary benefits were calculated separately for the healthcare and employment sectors for each year and based on the same number of individuals in the calculation of industry benefits. This ensured that benefits accruing to the healthcare and employment sectors were directly linked with the population receiving therapy. While benefits to industry could be estimated directly from the Information Management System data, there was no source of data allowing for the estimation of healthcare and employment sectors benefits. Alternatively, a dynamic Markov model was developed to estimate these benefits. Because the revenues to industry reflect the drug expenditure of payers, we did not include the drug costs in the benefits to the healthcare and employment sectors to avoid double-counting. (Monetary benefits were not net monetary benefits.)

Model Structure. All analyses were conducted using Microsoft Excel 2003 and TreeAge Pro 2009 (TREEAGE Software Inc; Williamstown, MA). The model included two arms, treatment versus no treatment (Figure 1), which were identical in terms of health states but different in terms of transition probabilities from hypercholesterolemia to other health states.

Patients begin each arm in the hypercholesterolemia health state. Over each year (i.e., model cycle), patients could experience no event, a stroke, an AMI, or die from a cardiovascular cause (cardiovascular disease [CVD] death). Patients who experience a stroke may die, recover (back to the hypercholesterolemia health state), or recover but experience long-term morbidity (the post-stroke health state). Patients who experience an AMI may die or recover in the post-AMI health states. Patients in the post-stroke, or post-AMI health states may experience no event, a subsequent event or die.

We excluded deaths from other causes, because there was no evidence to expect a difference in the risk of death from other causes between the two arms.

Model Inputs. Input estimates for the population receiving therapy were derived from the Information Management System data as shown in Figure 2 (bar chart). The studied population increased from 36 in 1990 to approximately 900,000 in 2003 and then decreased to approximately 400,000 in 2009. Our analysis allowed for new patients to enter and old patients to leave the model so that we could account for the increasing and decreasing hypercholesterolemia population prescribed simvastatin between 1990 and 2003 and between 2003 and 2009, respectively. We also adjusted for patient compliance with therapy. That is, benefits from therapy were only accrued to that proportion of patients who complied with therapy. A compliance rate of 75 percent (12) (range, 50–100 percent) was used in this study.

We did a systematic review and meta-analysis to estimate efficacy of simvastatin. Efficacy of simvastatin on stroke, AMI, and CVD death (Table 1) was pooled from five randomized controlled trials, including the Scandinavian Simvastatin Survival Study (24), the Heart Protection Study (16), the Simvastatin/Enalapril Coronary Atherosclerosis Trial (30), the Multicenter Anti-Atheroma Study (19), and the Multicenter Coronary Intervention Study (4). Other transition probabilities in the model were derived from literature as shown in Table 1.

Healthcare costs of stroke, AMI, and CVD death were derived from a systematic literature review of Canadian

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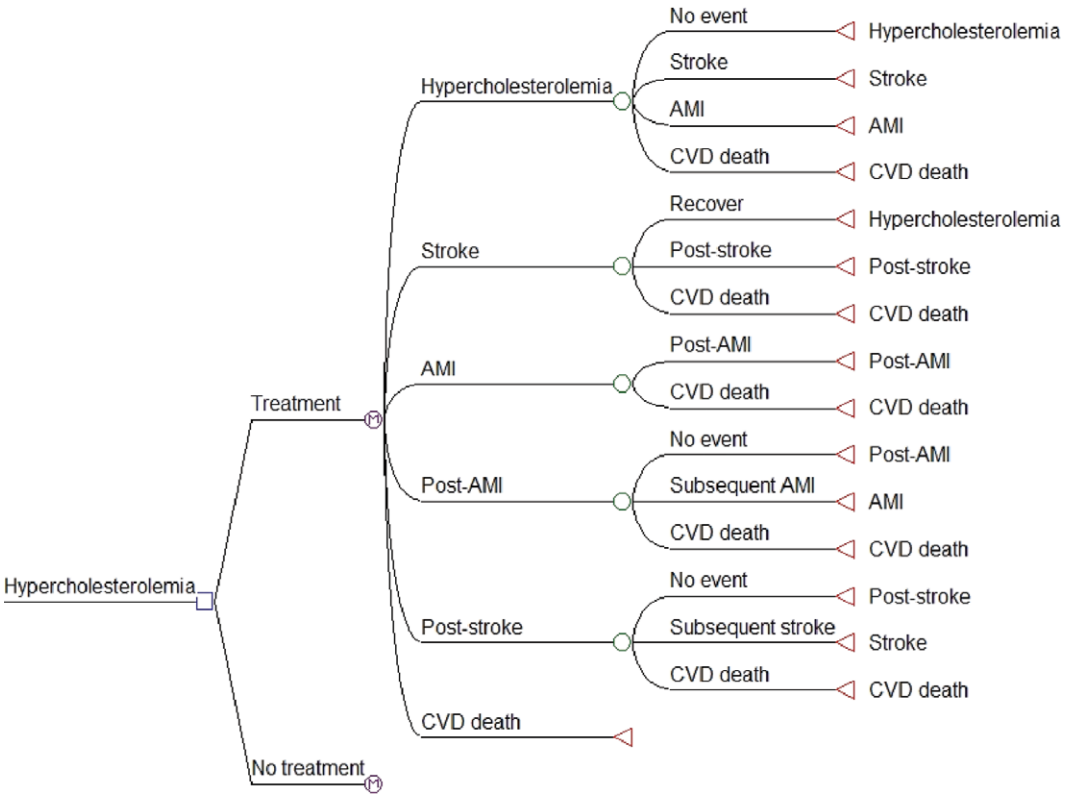

Figure 1. Model structure. AMI, acute myocardial infarction; CVD, cardiovascular disease.

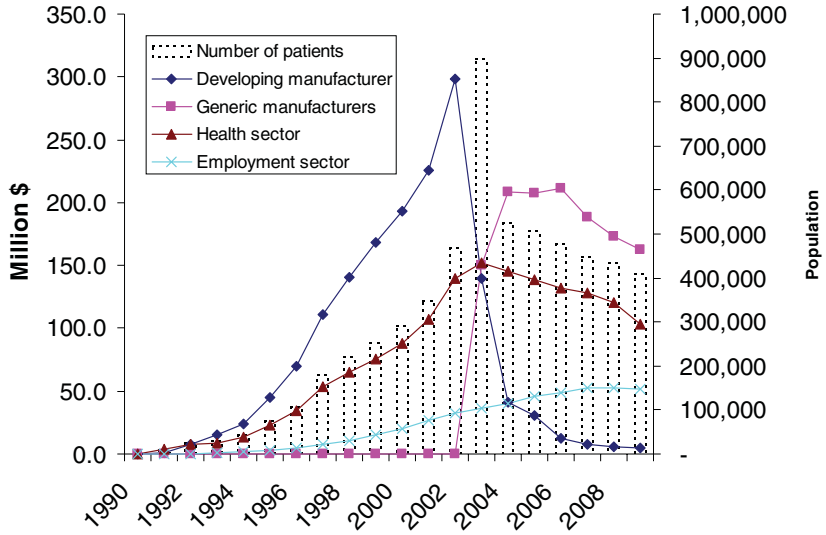

Figure 2. Yearly benefits and number of population on simvastatin.

studies (Table 1). When a cost for a single input was found in more than one source, an average cost between the studies was used.

Healthcare costs of the hypercholesterolemia, post-stroke, and post-AMI health states were estimated as a sum of costs for hospital days, for general practitioner and for specialist visits of people living with those conditions. Costs for hospital days and general practitioner or specialist visits were estimated by multiplying the average numbers of hospital days and general practitioner or specialist visits with the unit costs of a day or a visit, respectively (Table 1). The average numbers of hospital days and general practitioner and specialist visits were estimated from 2005 Canadian Community Health Survey by multivariate linear regressions controlling for demographic (i.e.,

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Table 1. Annual Transition Probabilities and Average Costs of Health States

Health states		Probability		
From	To	Simvastatin	Placebo	Data sources
Hypercholesterolemia				
	Hypercholesterolemia	#	#	
	Stroke	0.0082 (0.0067–0.0099)	0.0108 (0.0092–0.0129)	(4, 16, 19, 24, 30)
	AMI	0.0147 (0.0128–0.0170)	0.0219 (0.0196–0.0248)	(4, 16, 19, 24, 30)
	CVD death	0.0141 (0.0122–0.0164)	0.0173 (0.0153–0.0200)	(4, 16, 19, 24, 30)
Stroke				
	Hypercholesterolemia	0.1000	0.1000	(15)
	Post-stroke	#	#	
	CVD death	0.0424	0.0424	(32)
AMI				
	Post-AMI	#	#	
	CVD death	0.0732	0.0732	(28)
Post-AMI				
	Post-AMI	#	#	
	AMI	0.0692	0.0692	(31)
	CVD death	0.0257	0.0257	(20)
Stroke-effected				
	Post-stroke	#	#	
	Stroke	0.0952	0.0952	(32)
	CVD death	0.0119	0.0119	(10)
CVD death				
	CVD death	1.0000	1.0000	

Cost and health service utilization inputs	Mean	Data sources
Cost per 1 year for		
Stroke	$47,068	(11, 21, 22)
AMI	$21,256	(22, 23)
CVD death	$10,425	(13)
Cost per 1 day in hospital for		
Post-stroke	$1,030	(2)
Post-AMI	$1,213	(2)
Hypercholesterolemia	$871	(2)
Cost per general practitioner visit	$36	(3)
Cost per specialist visit	$51	(3)
Wage per day for		
Full-time	$182	(29)
Part-time	$122	(29)
Cost per CVD death per year for		
Full-time	$44,670	(29)
Part-time	$29,823	(29)

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Table 1. Continued.

Cost and health service utilization inputs	Mean	Data sources
Number of disability day per year for		
Post-stroke	26.12	CCHS 2005
Post-AMI	30.38	CCHS 2005
Hypercholesterolemia	14.96	CCHS 2005
Number of nights in hospital per year for		
Post-stroke	4.10	CCHS 2005
Post-AMI	3.66	CCHS 2005
Hypercholesterolemia	2.09	CCHS 2005
Number of general practitioners visits per year for		
Post-stroke	4.54	CCHS 2005
Post-AMI	4.58	CCHS 2005
Hypercholesterolemia	3.32	CCHS 2005
Number of specialist visits per year for		
Post-stroke	1.18	CCHS 2005
Post-AMI	1.54	CCHS 2005
Hypercholesterolemia	1.01	CCHS 2005

Note. Transition probability: The rates was estimated on an yearly basis and converted to probabilities using the formula: $p = 1\text{-}\exp(\text{-}rt)$, where p is a probability, r is a constant rate of an event over a time period t (6).
AMI, acute myocardial infarction; CVD, cardiovascular disease; CCHS, Canadian Community Health Survey.

sex, age, and marital status), socioeconomic (i.e., education, employment and family income), health behavior (i.e., physical activity and smoking status), and health status (i.e. other chronic diseases and mental health problems) variables. The unit costs per hospital day, per general practitioner visit, or specialist visit were derived from Alberta Health Costing 2006 (2) and Alberta Schedule of Medical Benefits 2010 (3).

We estimated the costs of lost productivity using a human capital approach (17). Full- and part-time workers were analyzed separately. The number of worker was estimated by multiplying the number of people aged 15–64 years with the labor participant rate (67.42 percent) and with the employment rate (93.3 percent) (29). These rates were estimated by averaging the corresponding yearly rates between 2000 and 2009 in Canada. Of the workers, 18 percent were part-time (17) and 64 percent were 45–64 years old (estimated from 2005 Canadian Community Health Survey data).

Lost productivity due to disability was equal to the number of disability days multiplied by the average Canadian wage per day. The number of disability days was estimated from 2005 Canadian Community Health Survey using a multivariate linear regression, which controlled for demographic and socioeconomic characteristics, health behavior and health status of the patients.

Lost productivity due to the premature death was equal to the number of years lost multiplied by the average annual income. Because of the 20-year time horizon, we counted the death of workers aged 15–44 years to be 20 years lost, and for persons aged 45–64 years, it was 10 years lost.

Details on estimated inputs of cost, healthcare usage, and disability day are shown in Table 1. All costs and benefits are expressed in 2010 Canadian dollars based on the Canadian consumer price index. Discounting was not included because the study examined the monetary benefits year by year as they occurred and not evaluating the value of benefits back to the date of introduction to simvastatin. Furthermore, discounting is applied for future benefits; the current analysis was retrospective in that the benefits have already occurred.

Sensitivity Analysis

Sensitivity analysis was conducted on two key input parameters, including compliance rate and drug efficacy. Compliance rate was varied between 50 and 100 percent. The drug efficacy was varied using the 95 percent confident intervals listed in Table 1.

RESULTS

The cumulative monetary benefits of simvastatin over the 20-year time horizon (1990–2009) were estimated at $4.8 billion (Table 2). Of this, developing manufacturer and healthcare sector accounted for the largest shares (32 percent each), followed by generic manufacturers (27 percent) and employment sector (9 percent). The trends of yearly monetary benefits differed

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Table 2. Cumulative Monetary Benefits for Different Beneficiaries (Million $; % of Total)

	Developing manufacturer	Generic manufacturer	Healthcare sector	Employment sector	Total
	Cumulative monetary benefits				
#	1,542.2	1,302.1	1,538.3	450.0	4,832.6
%	31.9%	26.9%	31.8%	9.3%	100.0%
Sensitivity analysis					
Compliance rate					
Worst (50%)	1,542.2	1,302.1	1,025.6	300.0	4,169.8
	37.0%	31.2%	24.6%	7.2%	100.0%
Best (100%)	1,542.2	1,302.1	2,051.1	600.0	5,495.4
	28.1%	23.7%	37.3%	10.9%	100.0%
Efficacy					
Lower	1,542.2	1,302.1	1,070.3	217.1	4,131.6
	37.3%	31.5%	25.9%	5.3%	100.0%
Higher	1,542.2	1,302.1	2,079.7	709.7	5,633.7
	27.4%	23.1%	36.9%	12.6%	100.0%

among the beneficiaries (Figure 2). The benefits to developing manufacturer dropped from 2002 when the pharmaceutical was no longer under patent protection when the benefits to generic manufacturers started to increase. Specifically, the benefits to developing manufacturer dropped from $298 million in 2002 to $5 million in 2009, while the benefits to generic manufacturer increased from $0 to $212 million in 2006 and then decreased to $163 million in 2009. The benefits to healthcare sector increased from 1990 ($0.3 million) to 2003 ($152 million) and then started to decrease from there (to $104 million in 2009), corresponding to the decreasing number of patients using simvastatin. The benefit to employment sector increased from $0 in 1990 and peaked at $52 million in 2007 and 2008 (Figure 2).

The sensitivity analysis for variations of the compliance rate showed that corresponding with the range from 50 percent to 100 percent, the cumulative monetary benefits of simvastatin varied from $4.2 to $5.5 billion (Table 2). Of this, developing manufacturer accounted for 28–37 percent, generic manufacturers 24–31 percent, healthcare sector 25–37 percent, and employment sector 7–11 percent. The variations in the efficacy of drug on prevention of stroke, AMI, and CVD death resulted in a variation of the cumulative monetary benefits from $4.1 billion to $5.6 billion, of which developing manufacturer accounted for 27–37 percent, generic manufacturers 23–32 percent, healthcare sector 26–37 percent, and employment sector 5–13 percent. Of note, the higher the compliance rate or the efficacy, the larger the share of the benefits to healthcare and employment sectors and vice versa for the share of the benefits to developing and generic manufacturers. This was because the absolute benefits to healthcare and employment sectors increased with the increase of the compliance rate or the efficacy, while the absolute benefits to developing and generic manufacturers did not change.

DISCUSSION

In this study, we estimated the societal monetary benefits of simvastatin and its distribution among the developing manufacturer, generic manufacturers, healthcare sector, and employment sector. The results indicated that monetary benefits were significant and experienced differently by the beneficiaries. Monetary benefits of simvastatin from 1990 to 2009 was estimated at $4.8 billion, of which, developing manufacturer and healthcare sector accounted for the largest shares (32 percent each), followed by generic manufacturers (27 percent) and employment sector (9 percent). Sensitivity analysis showed the higher the compliance rate or efficacy, the larger the benefits to healthcare and employment sectors, while the benefits to industry was unchanged.

Patent protection plays a vital role regarding monetary benefits to developing and generic manufacturers. During the patent protection period, the developing manufacturer accounts for the greatest share of industry benefits, while generic manufacturers account for the greatest share of industry benefits soon after patent expiration. This finding is not surprising, because the patents are to appropriate and promote the innovation by providing the right to exclude others from making, using, or selling an invention (8). Our study indicates that the patent period for simvastatin since market entry is approximately 12 years, which is consistent with the late 1990s regulatory conditions which stipulated that the basic statutory patent life is 20 years where approximately 12–13 years remain by the time commercial marketing is allowed (27). To have an appropriate length of patent period that promotes industry to both innovate and reduce the healthcare expenditure is crucial.

During the study time horizon, the benefits to developing manufacturer and healthcare sector were equal and accounted for the largest share of the cumulative monetary benefits (32 percent each). The trend of yearly benefit suggests that the healthcare sector's share will be larger than that of the developing manufacturer if the post-patent period is extended. However, it should be noted that the benefits to the healthcare sector started to decrease from 2003 (1 year after patent expiry) as a result of a decreasing population taking simvastatin during the same time period. This is possibly explained by other competitors entering the market.

During the study time the monetary benefits ratio between pharmaceutical industry (developing manufacturer + generic manufacturers) and other sectors in society (healthcare sector + employment sector) was approximately 6:4. This ratio will be changed (the other sectors' share will increase) if the used postpatent period in the model was extended and/or the societal benefits in terms of health-related quality of life improvement and/or the manufacturing costs of simvastatin and/or the costs of

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"unsuccessful" drugs to industry are included. For example, if producer surplus of statins is 80 percent and 20 percent of retail revenues before and after the patent expiration, respectively (18), the ratio will be reversed to be 4:6. In addition, Lindgren and Jonsson (18) show the consumer benefits are much higher than producer benefits when intangible benefits, such as quality-adjusted life-years gained or life-year gained, are included and transferred to monetary values.

In the Canadian pharmaceutical market, the annual cost of the generic alternative patient has been on average from 45 percent to 60 percent of the brand name simvastatin annual patient cost between 2000 and 2002, with public plans paying approximately 20 percent more than private plans and out-of-pocket patients. Following the same kind of policies that pharmacies are expected to offer patients generic alternative to brand name product, the use of generic drugs has been very dominant right after the patent expired. In comparison, in countries like Sweden, where the least expensive generic statins are marketed at approximately 5–10 percent of brand name original price (18), the users of simvastatin in Canada started to decrease from 2003, while the number of users in Sweden more than doubled during the same time after patent expired there. High pricing of simvastatin in Canada has likely influenced some patients to move to use other new cholesterol lowering drugs or not to continue to use them. This has likely influenced that the monetary benefits of the generic manufacturers are higher in Canada compared with many other countries and that the benefits of the healthcare and employment sectors are lower than expected.

This study has some limitations that should be acknowledged. First, the societal monetary benefits may be underestimated due to lack of public data in some provinces (British Columbia, Northwest Territory, and Nunavut) and exclusion of the patient benefits in terms of health-related quality of life improvement. Exclusion of the health-related quality of life was done because simvastatin is not expected to have any major direct impact on health-related quality of life, but those impacts are expected to happen indirectly through reduction of AMIs and strokes. Because those monetary transformations can produce very high dollar values that are difficult to interpret, we have left them out of this study. Second, the benefits to developing and generic manufacturers may be overestimated due to lack of data on manufacturing costs, costs of "unsuccessful" drugs, and other costs including wholesale/pharmacy markup, although we included the original development costs of simvastatin and the contribution toward further R&D. The manufacturing costs are difficult to estimate because no publish data is available. Lindgren and Jonsson (18) estimated that manufacturing sales and marketing costs would be approximately 20 percent of the brand name drug revenues. Third, there is no variable that directly identifies patients with hypercholesterolemia in Canadian Community Health Survey data, so hypercholesterolemia was defined as those who used hypercholesterolemia medications or people who chose to avoid foods with higher cholesterol. Fourth, populations in randomized controlled trials may not be representative of the general population with hypercholesterolemia. Finally, efficacy estimates from randomized controlled trials may not reflect real world, although we did take into account patient compliance.

In summary, the results indicate that the societal monetary benefits of innovative pharmaceuticals like simvastatin are significant and experienced differently by several beneficiaries. Patent protection, compliance to treatment, and efficacy play a vital role regarding the monetary benefits. High pricing of the generic products after the patent has expired seem to have significant impact on the development of the long-term usage of the effective drug and may impact on significant losses of benefits for healthcare and employment sectors, as well as patients. It is important to consider the monetary benefits to all beneficiaries separately and overtime when assessing the value of pharmaceutical innovation.

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CONFLICTS OF INTEREST

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