Do faster drug approvals increase safety risks? Evidence from Canada and Europe 2003-2012

Author
Nigel SB Rawson, Ph.D.

Publication Date
August 14, 2014.

Citation
Rawson NSB (2014). Do faster drug approvals increase safety risks? Evidence from Canada and Europe 2003-2012. *Canadian Health Policy*, August 14, 2014. Toronto: Canadian Health Policy Institute.

SUMMARY

Introduction
Before any new drug can be sold in Canada, it must be approved as safe and effective by Health Canada. Research shows that the wait for new drug approval in Canada has tended to be longer than in other jurisdictions. However, Health Canada's performance has been improving in recent years and the regulatory delays affecting access to new drugs have shortened substantially in Canada. Some experts have been critical of Health Canada's efforts to achieve more timely regulatory approval of new drugs and have argued that shorter review times will result in lower quality assurance for drug safety. This paper presents new evidence to examine whether, in fact, faster drug approvals have resulted in increased discontinuations of new drug products from the market for a safety reason.

Objective
To compare review times of new drugs approved Canada and Europe over a 10-year period (2003-2012) and the rate of drugs discontinued for safety reasons.

Data
Data were obtained from Health Canada and the European Medicines Agency.

Results
Over the 10-year period from 2003 to 2012, 186 new therapeutic drug products were approved by Health Canada compared with 189 by the European Medicines Agency. The median approval delay for the new drugs approved in Canada was 391 days compared with 338 days for new drugs approved in Europe. However, the rate of discontinuation of these new drugs for safety reasons was 1.6% in both jurisdictions. A comparison of jurisdictional experience between consecutive five-year periods showed that the Canadian median review time exceeded the European median by more than 100 days in drugs approved between 2003 and 2007 (503 days versus 349 days), but between 2008 and 2012, the Canadian median delay was only 15 days longer than the European median (353 days versus 338 days). Between the 2003-07 and 2008-12 periods, major decreases were seen in the Canadian median review times for drugs in the biotechnology (467 days), cardiovascular (218 days), endocrine and metabolic (202 days), and "other" categories (252 days). Despite shorter review times in Canada in 2008-12, none of the drugs approved during this period in either jurisdiction had been discontinued for a safety reason as of the end of June 2014, at which time they had a minimum of 18 months post-approval time. The rate of discontinuation in drugs approved in the 2003-07 period among products with a minimum of 18 months of post-approval time was also virtually the same in Canada (2.2%) and Europe (2.1%), in spite of the longer approval times in Canada during the period.

Conclusions
The wait for new drug approvals in Canada has been persistently longer than in Europe. However, new drug approval times in the two jurisdictions in the last five years grew closer than in the previous period due to Health Canada reducing its regulatory delays. Contrary to the suggestion that decreasing drug review times increases the risk of safety issues, the evidence shows that faster drug approval times in Canada were associated with a reduction in the rate of drugs discontinued for safety reasons versus the previous period (falling from 2.2% in 2003-07 to 0% in 2008-12). In addition, despite Europe having faster drug approval times than Canada throughout the decade, the rate of discontinuation for safety reasons was no higher in Europe than in Canada in any period. This means that the added drug approval delay in Canada achieved no extra assurance of safety but imposed a cost on Canadian patients who were forced to forego the potential health benefits that could have been gained from earlier access to new drugs.

INTRODUCTION

The extent of the time taken to review new drugs in Canada has been of concern since at least the mid-1980s. Analyses of drug approvals in the 1990s and early 2000s demonstrated that Canada had longer review times than those in the United States, the United Kingdom, and Sweden.[1] [2] [3] However, a recent analysis of 454 therapeutic drugs approved in both Canada and the United States between 1992 and 2011 found that, although the median approval time in Canada was considerably longer than in the United States between 1992 and 2006, the median approval times in the two countries were closer in 2007-2011 (356 days in Canada versus 302 days in the United States).[4]

Comparisons with the United Kingdom and Sweden were not pursued after 2001 as the European Medicines Agency (EMA), which began operating in 1995, took over the review of greater numbers of new drugs through its centralized and mutual recognition review procedures.[5] The gradual change from country specific reviews to these procedures made comprehensive data collection difficult.

The centralized procedure is now compulsory for:

a) Drugs for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases,
b) Drugs derived from biotechnology processes, such as genetic engineering,
c) Advanced-therapy medicines, such as gene-therapy, somatic cell-therapy or tissue-engineered medicines, and
d) Officially designated "orphan medicines," i.e. drugs used for rare human diseases.

In addition, manufacturers have the option of submitting an application to the centralized procedure if a drug is **a** significant therapeutic, scientific or technical innovation, or if it would be in the interest of public health. The mutual recognition procedure allows drugs approved in one member country to be approved by other members.[6]

The marketing approval of the majority of drugs in Europe is now obtained through the EMA and has been for some years.[7] Thus, sufficient time has elapsed between 2003 and 2012 for an analysis of review times in Canada and the European Union to be a valid comparison.

DATA

Data on new drugs approved in Canada between 2003 and 2012 were obtained from Health Canada's annual performance reports. Until recently, these were published on the agency's website but are now only available by direct request.[8] Because submission dates were not included in the reports until 2007, they were obtained directly from Health Canada. Once Health Canada approves a drug by providing a Notice of Compliance (NOC), it can be marketed in the country. Each drug's approval time was calculated as the difference between the submission and NOC dates in calendar days.

Information for drugs approved in Europe in the same 10-year period was identified from the EMA website.[9] This included drugs approved through the centralized procedure and some that were approved via the mutual recognition procedure. Before a drug can be marketed in

[1] Rawson et al (1998).
[2] Rawson (2000).
[3] Rawson (2003).
[4] Rawson (2013a).
[5] EMA (2014a).
[6] EMA (2014a).
[7] Downing et al (2012).
[8] Health Canada (2014).
[9] EMA (2014b).

the European Union, two actions are required. First, the EMA Committee for Medicinal Products for Human Use must issue a positive opinion on the marketing authorization and, second, the European Commission must adopt that opinion. To evaluate the efficiency of the EMA review process for comparison with Health Canada, the approval time was calculated as the number of calendar days between the submission date and the date of the EMA's positive opinion, as others have done.[10] [11] The date of adoption by European Commission was not used because this step is purely an administrative action that delays access in Europe by an additional two to three months.

A "new drug" was defined to be any new therapeutic drug of chemical or biologic origin. This definition excluded new salts, esters, dosage forms and combinations of previously approved drugs as well as diagnostic products. Vaccines were also excluded.

No account was taken of approval cycles or any period in which the regulatory clock was stopped in this analysis. Median and range of approval times were used as summary statistics due to the non-symmetric nature of the majority of the data.

Drugs discontinued for safety reasons were identified for Canada from earlier work[12] and Health Canada's website.[13] The EMA's websites were used to identify comparable data for Europe.[14] [15] A drug was regarded as being discontinued if all forms and doses were removed from the market. The rates of drugs discontinued for safety reasons in the two jurisdictions were compared.

[10] Roberts et al (2011).
[11] Downing et al (2012).
[12] Rawson (2013a).
[13] MedEffect Canada (2014).
[14] EMA (2014b).
[15] EMA (2014c).

RESULTS

Of 222 new therapeutic drugs approved between 2003 and 2012 that satisfied the study definition, 186 (83.8%) were approved by Health Canada and 189 (85.1%) by the EMA. Thirty-three drugs were approved in only Canada and were distributed across the decade relatively evenly, whereas 14 (39%) of the 36 drugs only approved in Europe received approval in 2012.

The overall median review times were 391 days in Canada and 338 days in Europe (Table 1). The median approval time in Canada was within 100 days of the European median in each category with the exceptions of drugs approved between 2003 and 2007 (Canada was longer by 154 days), biotechnology products (Canada was longer by 231 days), and endocrine and metabolic drugs (Canada was longer by 194 days).

Of the 222 drugs, 153 (68.9%) were approved in both jurisdictions (Table 2). Again, the Canadian median approval time was considerably longer than the European median for drugs approved in 2003-2007, biotechnology products, and endocrine and metabolic drugs, as well as "other" drugs.

When changes between the 2003-07 and 2008-12 periods were examined, the overall Canadian median review time decreased by 150 days to 353 days and by more than 200 days in the cardiovascular, endocrine and metabolic, "other," and biotechnology categories (218, 202, 252 and 467 days, respectively). It is also important to note that the maximum review time in Canada decreased from 1929 days in 2003-07 to 920 days in 2008-12. In Europe, there was only a modest decrease in review times between the two periods.

Only four drugs (efalizumab, lumiracoxib, rimonabant and sitaxsentan) of the 222 approved in either Canada or Europe between

2003 and 2012 were identified as having been discontinued for a safety reason by June 30, 2014 (Table 3) – at which time all 222 drugs had marketing approval for at least 18 months. Rimonabant was not approved in Canada and lumiracoxib was not approved in Europe. Therefore, the rate of discontinuation for safety reasons was 1.6% in both jurisdictions.

Lumiracoxib, rimonabant and sitaxsentan were discontinued within five years of their respective approval dates (Table 3). Efalizumab was discontinued just over five years after its marketing approval.

None of the drugs approved in 2008-12 had been discontinued for a safety reason as of the end of June 2014, at which time they had a minimum of 18 months post-approval time. In contrast, the rate of discontinuation in drugs approved in 2003-07 with a minimum of 18 months of post-approval time was 2.2% in Canada and 2.1% in Europe.

DISCUSSION

This study of 222 new therapeutic drugs approved in Canada and Europe over a 10-year period demonstrates that review times in Europe have been consistent over the decade and are also consistent with those attained by the agencies of the United Kingdom and Sweden in the 1990s.[16] [17] [18] It further shows that approval times were much longer in in Canada in 2003 to 2007 (as they were in 1992-2002) but have decreased in 2008 to 2012 so that they are now similar to those in Europe. These results are consistent with an analysis published in 2012[19] and are more reliable since the authors were unable to identify appropriate dates for many products approved in Canada.

The reduction in review times in Canada was most dramatic in biotechnology products (from a median time of 828 days in 2003-07 to 356 days in 2008-12). Since there has been a substantial increase in the number of novel biotechnology products in the last decade (many of which are intended for uncommon cancers or rare disorders for which there is either no therapy or the current treatment has limited effectiveness), this decrease is an important step forward for Canadian patients. Smaller but still considerable decreases occurred in cardiovascular, endocrine and metabolic, and "other" categories of drugs.

Despite this reduction, it is important to note that new drugs do not become marketable as early as they do in Europe. As Figure 1 shows 64% of the drugs approved in both Canada and Europe were submitted in Canada either before submission in Europe or within 180 days after the European submission. However, less than half that percentage (31%) received approval in Canada before or within 180 days after EMA approval. These figures changed little when restricted to drugs approved in Canada in 2008-12.

Although delaying access to new important drugs can have a major negative impact on patient health,[20] concern has been expressed that more rapid drug approvals may lead to an increased risk of safety issues.[21] [22] The number of drugs discontinued for safety reasons is small and not static, although the evidence used to support decisions about withdrawal has improved in the last decade.[23] The overall rate of discontinuation for safety reasons was 1.6% in both countries, which is less than previous estimates of 2-4%.[24] [25] [26] In the United States (a country with significantly shorter review times

[16] Rawson et al (1998).
[17] Rawson (2000).
[18] Rawson (2003).
[19] Downing et al (2012).
[20] Rawson (2013b).
[21] Lexchin (2012).
[22] Moore and Furberg (2012).
[23] McNaughton et al (2014).
[24] Rawson and Kaitin (2003).
[25] Begosh et al (2006).
[26] Lexchin (2014).

than Canada or Europe), the overall rate of discontinuation for safety reasons in the same period was even lower at 0.8%.

When limited to drugs with a post-approval period of at least 18 months, the rate of discontinuation in drugs approved between 2003 and 2007 (when Canada had much longer review times than Europe) was just over 2% in both Canada and Europe, but in 2008-12, when Canada had reduced its review times, the rate of discontinuation was 0% in both jurisdictions. Thus, contrary to the suggestion that decreasing drug review times increases the risk of safety issues, there has, in fact, been a reduction in the rate of drugs discontinued for safety reasons in recent years. This means that the added drug approval delay in Canada achieved no extra assurance of safety but imposed a cost on Canadian patients who were forced to forego the potential health benefits that could have been gained from earlier access to new drugs.

After many years of slower approval times, overall new drug review times in Canada in the last five years were close to those in Europe, although access to many drugs remains slower in Canada compared with Europe. There is no evidence that the decrease in review times has led to an increase in drugs discontinued for safety reasons.

REFERENCES

Begosh A, Goldsmith J, Hass E, Lutter RW, Nardinelli C, Vernon JA (2006). *Black box warnings and drug safety: examining the determinants and timing of FDA warning labels*. NBER Working Paper No. 12803. Cambridge, MA: National Bureau of Economic Research, 2006. http://www.nber.org/papers/w12803.

Downing NS, Aminawung JA, Shah ND, Braunstein JB, Krumholz HM, Ross JS (2012). Regulatory review of novel therapeutics – comparison of three regulatory agencies. *N Engl J Med* 2012; 366: 2284-93.

Health Canada (2014). Drug submission performance reports. Ottawa: Health Canada, 2014. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/docs/perform-rendement/index-eng.php.

EMA (2014a). Central authorisation of medicines. London: EMA, 2014. http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000109.jsp&mid=WC0b01ac0580028a47.

EMA (2014b). European public assessment reports. London: EMA, 2014. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124.

EMA (2014c). Patient safety. London: EMA, 2014. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/pha_listing.jsp&mid=WC0b01ac058001d126.

Lexchin J (2012). New drugs and safety: what happened to new active substances approved in Canada between 1995 and 2010? *Arch Intern Med* 2012; 172: 1680-1.

Lexchin J (2014). How safe are new drugs? Market withdrawal of drugs approved in Canada between 1990 and 2009. *Open Med* 2014; 8: e14-8.

McNaughton R, Huet G, Shakir S (2014). An investigation into drug products withdrawn from the EU market between 2002 and 2011 for safety reasons and the evidence used to support the decision-making. *BMJ Open* 2014; 4: e004221.

MedEffect Canada (2014). Ottawa: Health Canada, 2014. http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php.

Moore TJ, Furberg CD (2012). The safety risks of innovation: the FDA's expedited drug development pathway. *JAMA* 2012; 308: 869-70.

Rawson NSB (2000). Time required for approval of new drugs in Canada, Australia, Sweden, the United Kingdom and the United States in 1996-1998. *CMAJ* 2000; 162: 501-4.

Rawson NSB (2003). Timeliness of review and approval of new drugs in Canada from 1999 through 2001: is progress being made? *Clin Ther* 2003; 25: 1230-47.

Rawson NSB (2013a). New drug approval times and safety warnings in the United States and Canada, 1992-2011. *J Popul Ther Clin Pharmacol* 2013; 20: e67-81.

Rawson NSB (2013b). Potential impact of delayed access to five oncology drugs in Canada. Vancouver: Fraser Institute, November 2013.

Rawson NSB, Kaitin KI (2003). Canadian and US drug approval times and safety considerations. *Ann Pharmacother* 2003; 37: 1403-8.

Rawson NSB, Kaitin KI, Thomas KE, Perry G (1998). Drug review in Canada: a comparison with Australia, Sweden, the United Kingdom, and the United States. *Drug Inform J* 1998; 32: 1133-41.

Roberts SA, Allen JD, Sigal EV (2011). Despite criticism of the FDA review process, new cancer drugs reach patients sooner in the United States than in Europe. *Health Aff (Millwood)* 2011; 30: 1375-81.

ACKNOWLEDGEMENTS

The analysis, conclusions and opinions expressed in this paper are the author's own independent research and ideas. The author is the guarantor of the integrity and originality of the work.

ABOUT THE AUTHOR

Dr. Nigel SB Rawson (Ph.D., M.Sc.) is President of Eastlake Research Group in Oakville, Ontario and an affiliated scholar with Canadian Health Policy Institute. Dr. Rawson is a pharmaco-epidemiologist and pharmaceutical policy researcher. He has also been a Sessional Faculty member in the DeGroote School of Business at McMaster University. Educated in the United Kingdom, he holds an M.Sc. in statistics from the University of Newcastle-upon-Tyne and a Ph.D. in pharmaco-epidemiology from the University of Southampton. Dr. Rawson has performed epidemiologic studies of the use of drugs and their outcomes for over 30 years and published more than 100 book chapters and articles in peer-reviewed journals. He held academic research positions in the Universities of London and Southampton in the United Kingdom until the end of 1989, when he became a research scientist at the University of Saskatchewan and later Merck Frosst/MRC Research Professor in Pharmaco-epidemiology. He was subsequently Professor of Pharmaco-epidemiology at Memorial University of Newfoundland. His research activities focused on population-based studies of the use and safety of drugs using administrative healthcare utilization data and the evaluation of issues impacting access to new drugs. Dr. Rawson has also been a senior researcher in the Center for Health Care Policy and Evaluation, an independent research team in United Health Group (one of the largest health insurers in the United States), where he collaborated with the Food and Drug Administration on drug safety studies, and GlaxoSmithKline's only epidemiologist in Canada providing advice and analysis for the company's current and developing medicines and vaccines. Dr. Rawson established Eastlake Research Group in 2012 with a mission to create data-driven responses to pharmaceutical and health policy issues.

DATA TABLES

Table 1: Review times in Canada v Europe for all drugs approved within each jurisdiction.

		Health Canada approval			EMA approval		
		No. of drugs	Median (days)	Range (days)	No. of drugs	Median (days)	Range (days)
Overall		186	391	196-1929	189	338	146-829
Approval period:	2003-2007	93	503	196-1929	95	349	148-829
	2008-2012	93	353	203-920	94	338	146-666
Product type:	Biotechnology	46	580	203-1929	45	349	183-675
	Small molecule	140	359	196-1902	144	338	146-829
Drug type:	Anti-infective	29	346	196-1790	29	349	148-638
	Cardiovascular	21	410	213-920	19	338	244-829
	CNS and psychiatric	23	503	271-1902	16	410	275-794
	Endocrine and metabolic	15	530	211-1235	18	336	184-465
	Musculoskeletal and pain	10	419	343-863	12	422	323-542
	Oncology	37	362	197-1490	40	331	167-556
	Respiratory and GI	9	349	206-1582	13	331	146-485
	"Other"	42	357	203-1929	42	351	183-666

EMA: European Medicines Agency; CNS: Central nervous system; GI: Gastrointestinal

Table 2: Review times in Canada v Europe for drugs approved in-common across both jurisdictions.

			HC approval		EMA approval	
		No. of drugs	Median (days)	Range (days)	Median (days)	Range (days)
Overall		153	386	196-1929	337	146-794
Approval period:	2003-2007	73	484	196-1929	334	146-675
	2008-2012	80	352	203-893	337	156-794
Product type:	Biotechnology	41	532	203-1929	334	183-675
	Small molecule	112	355	196-1790	337	146-794
Drug type:	Anti-infective	28	344	196-1790	341	148-638
	Cardiovascular	14	397	213-743	337	244-485
	CNS and psychiatric	14	434	304-805	415	275-794
	Endocrine and metabolic	14	589	211-1235	302	184-402
	Musculoskeletal and pain	8	476	343-863	380	323-512
	Oncology	34	371	197-1490	330	167-556
	Respiratory and GI	9	349	206-1582	331	146-485
	"Other"	32	461	203-1929	338	183-666

HC: Health Canada; EMA: European Medicines Agency; CNS: Central nervous system; GI: Gastrointestinal

Table 3: Review times and time between approval and discontinuation for drugs withdrawn for safety reasons in Canada or Europe

Drug	Health Canada				European Medicines Agency			
	Approval date	Review time (days)	Discontinuation date	Approval to discontinuation (days)	Approval date	Review time (days)	Discontinuation date	Approval to discontinuation (days)
Efalizumab	24/10/2005	921	11/06/2009	1326	23/06/2004	485	09/06/2009	1723
Lumiracoxib	02/11/2006	352	05/10/2007	337	Not approved			
Rimonabant	Not approved				27/04/2006	344	23/10/2008	857
Sitaxsentan	30/05/2007	583	20/12/2010	1300	01/06/2006	288	06/01/2011	1610

FIGURE 1: Difference between dates of submission to Health Canada and the European Medicines Agency (EMA) and difference between dates of approval by Health Canada and the EMA for drugs approved by both agencies.