

**How Safe Are New Drugs: Drugs Withdrawn from the Canadian Market Between  
January 1, 1990 and December 31, 2009**

Joel Lexchin is a Professor in the School of Health Policy and Management at York University in Toronto where he teaches health policy in general and pharmaceutical policy in particular. He also works in the emergency department at the University Health Network and is an Associate Professor in the Department of Family and Community Medicine at the University of Toronto. E mail: <jlexchin@yorku.ca>

Correspondence and guarantor (e mail address may be published):

Joel Lexchin MD  
School of Health Policy and Management  
York University  
4700 Keele St.  
Toronto, ON M3J 1P3  
Tel: 416-736-2100 x 22119  
Fax: 416-736-5227  
E mail: jlexchin@yorku.ca

## **Abstract**

### **Background**

Studying drugs withdrawn from the market for safety reasons can help in evaluating the strengths and weaknesses of the pre- and postmarket safety evaluation systems. This study looks at two questions: 1) has there been a change in the percent of new drugs that are eventually withdrawn because of safety reasons and 2) how long are new drugs on the market before their serious safety problems are recognized.

### **Methods**

All drugs marketed between January 1, 1990 and December 31, 2009 and subsequently withdrawn for safety reasons were identified and the generic name, date of approval and date of withdrawal were recorded. The total number of drugs approved between the same dates was obtained from annual Health Canada reports. The percent of NAS withdrawn in the 5-year periods 1990-1994, 1995-1999, 2000-2004 and 2005-2009 was compared using Chi-square. The time between approval and withdrawal was calculated in days.

### **Results**

528 new drugs were approved and of these 20 were withdrawn. Between 3.1 and 4.2% of the drugs approved in a 5-year period were eventually withdrawn ( $p = 0.954$ ). The median time between approval and withdrawal was 1242 days (interquartile range 636, 2290).

### **Interpretation**

The finding that there was no difference in the percent of drugs withdrawn in the four 5 year periods indicates that there has not been any weakening in the premarket evaluation system. The 1242-day median time between NOC and withdrawal emphasizes the need to

be particularly cautious in prescribing new drugs early in their lifecycle.

## **Introduction**

When a new active substance (NAS, a molecule that has never been marketed in Canada in any form) receives its Notice of Compliance (NOC, marketing approval) there is relatively little known about its safety profile. This situation exists for a number of reasons including the relatively homogeneous nature of the population enrolled in premarket clinical trials, the use of pre-randomization run-in periods, the short-term nature of many trials and the relatively small number of patients in these trials.

One measure of the limited initial information about safety is that just under one in four NAS eventually acquire either a serious safety warning (a warning in bolded black lettering and/or a boxed warning) or have to be withdrawn from the market because of safety concerns.<sup>3</sup> Drugs in the latter category are the ones with the most serious safety issues, as whatever their therapeutic benefits, they are too dangerous to remain on the market. Looking at this group of drugs can provide insights into the strengths and weaknesses of both the pre- and postmarket safety evaluation systems. Specifically, this study looks at two questions: 1) has there been a change in the percent of NAS, approved in 5 year periods between the start of 1990 and the end of 2009, that are eventually withdrawn because of safety reasons and 2) how long are NAS on the market before their serious safety problems are recognized. In addition, there are two secondary questions that are examined: 1) what is the period of time between when a drug is approved and it receives a first serious safety warning and 2) what is the period of time between a first safety warning and the eventual withdrawal of the drug.

## Methods

A list of all drugs withdrawn from the Canadian market between January 1, 1990 and December 31, 2009 was compiled from Lexchin<sup>4</sup> and Health Canada's MedEffect web site <<http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/index-eng.php>>.

Withdrawals of specific lots of a drug due to manufacturing problems were excluded.

This list was narrowed to those approved after the start of 1990 using the Notice of Compliance web site <<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/index-eng.php>>. For each of these drugs the following information was recorded: generic name, date of NOC and date of market withdrawal. In addition, the MedEffect web site was used to identify if the product received a serious safety warning prior to withdrawal and the date of the warning. Serious safety advisories issued because of misuse of a drug (e.g., an unapproved use) or medication errors (e.g., a warning about remembering to remove a transdermal patch before applying a second one) were excluded. When necessary, notices on the MedEffect web site were supplemented by searching on the product name in the Drug Product Database (DPD) <<http://webprod3.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp>>. For example, a notice that one product, gatifloxacin, had been withdrawn from the market never appeared on the MedEffect web site and the withdrawal was only confirmed on the DPD web site.

Troglitazone was approved but never marketed in Canada because of a dispute about its introductory price. There was no information about revocation of its NOC on the MedEffect web site. The drug was removed from the United States' market in March

2000 and March 15, 2000 was arbitrarily used as its withdrawal date in Canada. It was retained in the analysis because it was a product that was approved and then later shown to have side effects serious enough that it was withdrawn. The announcement about the withdrawal of cisapride made reference to a safety warning in February 2000 but the exact date was not stated and therefore was arbitrarily set as February 14. Amphetamine salts was withdrawn on February 9, 2005 but allowed back on market on August 24, 2005 and therefore not included in the list of drugs withdrawn for safety.

The total number of NAS approved in the 5 year periods (1990-1994, 1995-1999, 2000-2004, 2005-2009) was obtained from the annual reports of the Therapeutic Products Directorate (TPD) and the Biologic and Genetic Therapies Directorate (BGTD) (henceforth collectively referred to as the TPD) - available by directly contacting the directorates at <[publications@hc-sc.gc.ca](mailto:publications@hc-sc.gc.ca)>.

The percent of NAS withdrawn in the four 5-year periods was compared using Chi-square (AcaStat 8.2.3, AcaStat Software). The following time periods were calculated in days – NOC to first serious safety warning, NOC to withdrawal, first serious safety warning to withdrawal. Calculations were done with Excel 2011 for Macintosh (Microsoft Inc.)

There was no funding for this study.

## **Results**

A total of 528 NAS were approved between January 1, 1990 and December 31, 2009 and of these 20 were withdrawn. Between 3.1 and 4.2% of the drugs approved in a 5-year period were eventually withdrawn ( $p = 0.954$ ) (Table 1). Table 2 lists the 20 drugs; of these 11 first had a serious safety warning and 9 did not. The median time between NOC and withdrawal was 1242 days (interquartile range 636, 2290). For the 11 drugs with a prior safety warning, the median times between NOC and the warning and the warning and withdrawal were 907 days (interquartile range 196, 1525) and 329 days (interquartile range 119, 893), respectively. Two drugs (sitaxsentam and valdecoxib) received a safety warning 20 days after their NOC. Cerivastatin and lumiracoxib were withdrawn 23 and 48 days, respectively, after their safety warning.

### **Interpretation**

The finding that there was no difference in the percent of drugs withdrawn in the four 5 year periods is reassuring as it seems that there has not been any weakening in the premarket evaluation system. However, equally important is whether there has been a change in how many people are exposed to drugs before they are withdrawn. As an example, in 2003, the year before rofecoxib was removed from the market, it was the 10<sup>th</sup> most frequently prescribed medication in Canada.<sup>5</sup> Unfortunately, there is no publicly available data to answer this question.

The 1242-day median time between NOC and withdrawal emphasizes the need to be particularly cautious in prescribing new drugs early in their lifecycle. On-the-other hand, a prolonged period on the market is no guarantee of safety. It took over 16 years (5908

days) to recognize the problems with pergolide. The short time intervals between marketing approval and a serious safety warning and between a safety warning and withdrawal raise questions about both the pre- and postmarket safety evaluations. Was Health Canada unaware of the safety problems with sitaxsentam and valdecoxib when it approved these drugs? What changed in the few weeks between when a safety warning was issued about cerivastatin and lumiracoxib and when they were withdrawn? Nine of the 20 drugs that were withdrawn had no prior safety warning. Was Health Canada unaware of any safety issues associated with these products before they were withdrawn?

This study has several limitations. The definition of a serious safety warning was based on the way that Health Canada displayed the information (bolded black print and/or boxed text) but the criteria that Health Canada used in deciding on its safety warnings and the emphasis that it placed on any particular safety issue are not known. There were inconsistencies in the Health Canada databases. Some drugs identified as a NAS in the TPD annual reports were not called a NAS in the Notice of Compliance Online Query web site. The date on which a NAS receives a NOC is not necessarily the date on which the company actually decides to market the drug and therefore the length of time the drug is available before it receives a safety warning and/or is withdrawn may be shorter than what is reported here.

This research emphasizes the point that a small but not insignificant number of drugs that are approved will eventually be found to be too unsafe to remain on the market. It also



raises questions about the thoroughness of Health Canada's pre- and postmarket evaluation of drug safety.

## References

1. Rothwell P. External validity of randomised controlled trials: “to whom do the results of this trial apply?”. *Lancet*. 2005;365:82-93.
2. Ahmad S. Adverse drug event monitoring at the Food and Drug Administration: your report can make a difference. *Journal of General Internal Medicine*. 2003;18:57-60.
3. Lexchin J. New drugs and safety: what happened to new active substances approved in Canada between 1995 and 2010? *Archives of Internal Medicine*. 2012;172:1680-1.
4. Lexchin J. Drug withdrawals from the Canadian market for safety reasons, 1963 - 2004. *CMAJ*. 2005;172:765-7.
5. IMS Health Canada. *Top 50 Prescribed Medications\**, 2003, 2004.

**Table 1: Drugs withdrawn for safety reasons as a percent of all new active substances approved in a five-year period, January 1, 1990 to December 31, 2009**

	<b>Five year period</b>			
	<b>1990-1994</b>	<b>1995-1999</b>	<b>2000-2004</b>	<b>2005-2009</b>
<b>No. of new active substances approved</b>	129	166	119	114
<b>No. of withdrawals</b>	4	7	5	4
<b>Percent of new active substances withdrawn</b>	3.1	4.2	4.2	3.5

No difference between 5-year periods ( $p = 0.954$ )

**Table 2: Drugs withdrawn for safety reasons**

<b>Generic name</b>	<b>Date of NOC*</b>	<b>Date of first serious safety warning</b>	<b>Date of withdrawal</b>	<b>Days from NOC* to withdrawal</b>	<b>Days from NOC* to safety warning</b>	<b>Days from safety warning to withdrawal</b>
Pergolide	1991-06-27		2007-08-30	5908		
Cisapride	1991-08-15	2000-02-14	2000-08-07	3280	3105	175
Remoxipride	1993-07-26		1994-03-14	231		
Nefazodone	1994-04-27	2001-06-20	2003-11-27	3501	2611	890
Dexfenfluramine	1996-07-09	1996-10-21	1997-09-15	433	104	329
Troglitazone	1997-05-09		2000-03-15	1041		
Tolcapone	1997-10-08		1998-11-20	408		
Cerivastatin	1998-02-18	2001-07-16	2001-08-08	1267	1244	23
Grepafloxacin	1998-04-09		1999-10-26	565		
Trovaflaxacin	1998-12-04		2001-11-22	1084		
Rofecoxib	1999-10-25	2002-04-19	2004-09-30	1802	907	895
Sibutramine	2000-12-28	2002-03-27	2010-10-08	3571	454	3117
Gatifloxacin	2001-01-09	2005-12-19	2006-06-29	1997	1805	192
Tegaserod	2002-03-12		2007-03-30	1844		
Valdecocixib	2002-12-11	2002-12-31	2005-04-07	848	20	828
Drotrecogin alfa	2003-02-20		2011-10-25	3169		
Efalizumab	2005-10-24	2008-12-22	2009-02-22	1217	1155	62
Lumiracoxib	2006-11-02	2007-08-16	2007-10-03	335	287	48
Sitaxsentam	2007-06-19	2007-07-09	2010-12-15	1275	20	1255
Ceftobiprole	2008-06-26		2010-04-16	659		
<b>Median (interquartile range)</b>				1242 (636, 2290)	907 (196, 1525)	329 (119, 893)

\*NOC = Notice of Compliance