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Assessing Canada's Drug Shortage Problem

Drug shortages are a problem in need of solutions in Canada. About 1,000 shortages have been reported annually, affecting 1,250 products during a recent three-year period. A stable supply of a diversity of medicines is necessary to keep healthcare costs down and maintain access for the entire population.

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THE STUDY IN BRIEF

Drug shortages provoke great anxiety among patients who cannot obtain trusted medications for chronic conditions. For pharmacists and the care team, shortages demand time-consuming and often frustrating searches for alternatives. For patients, they result in the stress and harm of delayed treatments and surgeries. For governments, they increase healthcare expenditures to acquire the scarce products or their replacements from other sources or innovator substitutes. Some studies have shown that drug shortages might lead to illness and even premature death (Metzger, Billett, and Link 2012; United States 2015).

In this *Commentary*, we examine the size of the drug shortage problem in Canada between 2010 and 2017, scan the stated reasons for shortages internationally, and look at various proposed solutions. Approximately 1,000 shortages have been reported annually, affecting 1,250 products during a recent three-year period. Indeed, the number of shortages appears to be increasing, although this apparent rise might be explained by growing pressure to adhere to the policy of mandatory notification introduced in 2016, even if its enforcement is still lacking. The majority (77 percent) of drug shortages involve generic drugs, although a significant proportion (23 percent) also affected innovator drugs. These figures correspond to the relative prescription volume of generic and innovator drugs.

Several surveys by pharmacists, physicians and various specialties have documented the extent of the drug shortage affecting the majority of practitioners in every province, and find it present over a wide array of products (Canadian Pharmacists Association 2010, 2011; Hall et al. 2013; Sullivan 2014). The precise causes of Canadian drug shortages are unknown and little has been done to conduct root-cause analysis or explore the consequences of Canada's limited capacity to supply its needs for medicines with locally manufactured active ingredients and finished products.

Drug shortages are a global problem, although their manifestations vary among countries. Most countries do not measure them, but media sources report on individual crises as they emerge, detailing their effects on pressing health problems.

A stable supply solution of a diversity of medicines is necessary to keep healthcare costs down, avoid expensive solutions to sudden emergencies and maintain access to medications for the entire population, including the 10 percent of Canadians who cannot afford their prescription drugs (Law et al. 2012).

We hope that regular analysis of the drug shortage problem will generate insight into the extent of the problem, its possible causes and provide a baseline for assessing the effectiveness of policies created to manage and prevent it. We urge Health Canada to provide annual reports on the drug shortage problem in an effort to define it, explain it and, above all, solve it. Only when the causes are identified can solutions be found.

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Since 2010, Canadian patients, physicians and pharmacists have been wrestling with drug shortages, mainly for generic drugs, which make up around 70 percent of Canadian prescriptions.

Shortages provoke great anxiety among patients who cannot obtain trusted medications for chronic conditions. For pharmacists and the care team, shortages demand time-consuming and often frustrating searches for alternatives. For patients, they result in the stress and harm of delayed treatments and surgeries. For governments, they increase healthcare expenditures to acquire the scarce products or their replacements from other sources or innovator substitutes. Some studies have shown that drug shortages might lead to illness and even premature death (Metzger, Billett, and Link 2012; United States 2015).

Several surveys by pharmacists, physicians and various specialties have documented the extent of the drug shortage affecting the majority of practitioners in every province and find it present over a wide array of products (Canadian Pharmacists Association 2010, 2011; Hall et al. 2013; Rinaldi et al. 2016, Sullivan 2014). In early 2012, two years into the problem in Canada, a crisis in the supply of some drugs, including injectable morphine and anesthetics, emerged when the US Food and Drug Administration (FDA) issued a warning letter to Sandoz Canada about quality-control issues. The company discontinued certain products and temporarily suspended manufacturing injectables at its production facility in Boucherville,

Quebec. A large public outcry provoked an emergency debate in the House of Commons on March 12, 2012, followed by three days of hearings by the House of Commons Standing Committee on Health. One result of these discussions was the broadly constituted Multi-Stakeholder Steering Committee on Drug Shortages (2017; see also Canada 2012). Another result was the creation of a website at which industry was to voluntarily post shortages, ideally in advance. This site was linked from Health Canada's website, but it was the joint responsibility of both the generic and innovative drug industries, which contributed to its costs. It was managed by the professional association of the research pharmaceutical industry, Rx and D Canada, now called Innovative Medicines Canada. On March 14, 2017, Health Canada took over the reporting site from industry by awarding a contract to Bell Canada. Notification became mandatory, and emails for those registered now come daily instead of every few weeks.

In this *Commentary*, we examine the size of the drug shortage problem between 2010 and 2017, scan the stated reasons for shortages internationally and look at various proposed solutions. Although hospital pharmacists have mitigated shortages locally, greater policy attention to prevent shortages altogether is needed in both community and

For assistance with information about websites cited in this *Commentary*, we are grateful to Keith McIntosh of Innovative Medicines Canada and Joanne Garrah and Eian Elliott, both of Health Canada. For helpful comments on an earlier version of this paper, we thank Jin-Hyeun Huh, Director of Pharmacy, University Health Network; Geneviève Pelletier of Pfizer Canada; Anne Wilkie of the Canadian Generic Pharmaceutical Association; Christian Ouellet of Sandoz Canada; HealthPRO; reviewers Tom Closson, Paul Grootendorst, Aidan Hollis, Jim Keon, Christian Ouellet; as well as Colin Busby and Rosalie Wyonch of the C.D. Howe Institute; members of the C.D. Howe Institute Health Policy Council; and anonymous reviewers. Jessy Donelle was supported by a research grant from Brian White-Guay, Université de Montréal.

hospital settings. The best options are accurate measurement in conjunction with mandatory reporting; clarity about and access to substitutes; revisiting and reinforcing the duty-to-supply clause in pharmaceutical licensing; and an international effort to understand the causes of shortages in an industry characterized by complex global supply chain arrangements both for generic and innovator products. Only when the causes are understood can robust policy decisions be made about management.

THE PROBLEM: ITS ORIGINS AND WHERE WE ARE NOW

Prior to the setting up of the drug shortages reporting website, much debate had focused on whether notification of shortages should be mandatory and be made in advance. Despite a unanimous vote in the House of Commons on March 14, 2012, for mandatory notification, the government of Stephen Harper opposed the policy, and later defeated a private member's bill to that effect. The inadequacies of the reporting website, meanwhile, became well known to health professionals: not all shortages were listed; most appeared on the list after the shortage had begun; some did not appear at all; substitutes were never suggested; causes were vague or hidden; information varied; and dates of resolution or discontinuation were obfuscated by archiving and "updating." Indeed, the site was open to revision, and the totals were in a state of flux. In fairness, the definition of a shortage was not clear and could range from temporary backorders to unavailability for an undefined duration. By law, the suggestion of substitute products was not a task for industry. Furthermore, the site was awkward to use and did not offer any periodic status report information on shortages. Interested parties could subscribe to

regular updates by e-mail message – initially weekly – detailing new products that had been added to (or removed from) the database.

On February 10, 2015, then health minister Rona Ambrose declared that mandatory notification would go into effect with a "name and shame" policy for manufacturers that failed to report shortages (Lunn et al. 2015),); however, since then, only two letters of failure to comply have been issued. Clinicians and pharmacists know that many more shortages have not been properly posted, though, in fairness, it is not always possible for manufacturers to know in advance when a shortage will emerge or to predict with accuracy when it will end. On May 19, 2016, the new minister of health, Jane Philpott, in the face of continued reports about the persistence of drug shortages, reiterated the mandatory notification policy, promised major changes to the reporting mechanism and announced the government's intention to take back the website, calling for tenders to find a third-party manager.¹ Consequently, after that date, the website's managers had little incentive to make major changes, and the definition of shortages remained vague. Nevertheless, over time, a series of technical improvements to the website facilitated data entry, with fields that populated automatically with like information from different companies, thus avoiding discrepancies and duplications that had characterized earlier entries. Independent of the reporting rate, however, the "content alert" e-mail updates sent to registered users declined: in 2014, they averaged four alerts each month; in 2015, it was 2.9; and in 2016, 1.6. During the first three months of 2017 only one message was sent.

Given the inadequacies of the reporting website, many Canadian healthcare professionals referred instead to US websites, including those of the

1 "Federal government orders mandatory reporting," *Canada Journal*, May 21, 2016, available online at <http://canadajournal.net/health/health-canada-to-require-drug-industry-to-report-shortages-47910-2016/>.

American Society of Health-System Pharmacists, the FDA, and the University of Utah College of Pharmacy, which until recently was open access. Some manufacturers, some provinces and some group purchasing organizations (GPOs) also have listed products in short supply. For example, since 2015, British Columbia has maintained a list of shortages (British Columbia 2018), and the large Ontario-based GPO, HealthPRO, has been attempting to measure the shortages (without publishing them) and requests regular inventory-holding surveys of critical drugs in an attempt to identify a potential supply disruption earlier.² Other sites also offered alternative drug suggestions, including two Canadian sites – one at the University of Saskatchewan and another run by the Quebec-based GPO, Sigma Santé – that later ceased operations and deferred to the drugshortages.ca site, which, because of legal constraints on the industry, was unable to suggest alternatives. None of these sites aimed to analyze the national situation in Canada with annual or monthly reports, nor did Health Canada ever supply numerical reports. Recently, a Montreal team reported on its measurement of drug shortages until 2014, relying on a spreadsheet that had been provided weekly or monthly from a single Canadian drug wholesaler, McKesson Canada; the report emphasized its predominant effects on cardiac drugs (Rinaldi et al. 2017).

On March 14, 2017, Health Canada released a new drug shortages website and finally put into effect a mandatory reporting policy. The site is operated, as noted, by Bell Canada under contract with Health Canada, rather than by industry. Some but not all of the old records were rolled over, searching was improved, a redirect was established from the old URL and e-mail updates are now sent daily. One problem is that, on the face page

of the database, the “start date” of each shortage is obliterated by the “most recent update,” making the duration seem shorter than it is. Only by opening each individual report can one find the start date. Consequently, tracing the history and duration of individual shortages is difficult. Reported numbers of shortages have increased, but it is unclear if these changes reflect actual increases, greater manufacturer compliance with improved reporting or the redefinition of what constitutes a shortage.

Indeed, the definition of a drug shortage in Canada continues to be a sore point with industry, which judges it to be too broad. According to the current definition, “[m]anufacturers will post all drug shortages, anticipated or actual as well as discontinuations, on drugshortages.ca, no less than six months in advance or if known less than six months in advance, it should be reported within five days from when they become aware of it, to allow maximum opportunity for the healthcare system to react to the shortage” (Multistakeholder Steering Committee 2017). The effect of the definition, industry claims, is to make Canada’s problem now appear to be much worse than in places that use a more restrictive definition or that do not mandate reporting. Under the current definition, some claim, temporary backorders at any step in the supply chain must be reported, creating an overreporting situation that leads to confusion for healthcare practitioners and undue alarm for patients.

Drug shortages are a global problem having differing manifestations and causes in different countries (International Pharmaceutical Federation 2017). In the United States, the FDA and the Government Accountability Office (GAO) have been measuring the extent of shortages annually since 2012. The US definition of a shortage is more restrictive than the definition now used in Canada: it excludes temporary backorders and is restricted

2 HealthPro, personal communication.

to products deemed to be “medically necessary,” the absence of which could “have a significant effect on public health” (United States 2014a). The designation of “medically necessary” entails recognition of whether or not a) the molecule is available through more than a single supplier; b) supplied in other dose formats; and c) considered an essential medicine (Eom, Grootendorst, and Duffin 2016; Morgan et al. 2015, 2017). In Canada, in contrast, with the exception of the one group report cited above (Rinaldi et al. 2017), no Canadian entities have attempted to measure drug shortages. Without an accurate measure of the nature and extent of the problem, it is impossible to characterize Canada’s situation or know if it resembles that in the United States or elsewhere. It is also difficult for policymakers to plan for the management of shortages in the short term or to generate procedures to prevent them in the future.

MEASURING DRUG SHORTAGES IN CANADA

To explore the history and nature of the Canadian drug shortage problem, we used data from three sources:

- the original Canadian drug shortage database,³ which had voluntary reporting of shortages of pharmaceutical products by manufacturing authorizations holders (MAHs) and was available from early 2012 until mid-March 2017;
- the current Canadian drug shortage database,⁴ which has been active since March 2017 and has mandatory shortage reporting; and

- the Health Canada Drug Products Database (DPD),⁵ which contains current and historical data on all drug products available in Canada.

In the original shortages database, Manufacturing Authorizations Holders (MAHs) were expected to report any product supply disruption likely to take at least 20 days to be resolved. Once a shortage was declared, the MAH was to update the database by indicating the estimated resupply date. We initially gathered data available on the website for all drug shortages reported between January 1, 2012, and December 31, 2016. We were later given an export of all of the original website data up until the site closed in March 2017. In the current shortage database, MAHs are required to report all shortages. Drug product discontinuations are now reported separately from shortages, so there is no direct way to link shortages with discontinuations from this new database. We gathered all shortage reports from the database as of December 31, 2017. The Health Canada DPD is updated daily and includes all drug products available in Canada. Every drug product is assigned a drug identification number (DIN)⁶ that uniquely identifies the manufacturer, dose and formulation of the product. A DIN uniquely identifies the following product characteristics: manufacturer; product name; active ingredient(s); strength(s) of active ingredient(s); pharmaceutical form; route of administration.⁷

The DPD organizes drugs with similar ingredients by assigning Ingredient Group numbers; it also provides historical tracking of drug products over time as to when they are approved,

3 Formerly available at www.drugshortages.ca.

4 Available at <https://www.drugshortagescanada.ca>.

5 Available at <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php>.

6 Two manufacturers with the same product in the same dosage will have two different DINs. Similarly, a manufacturer with a product in several different doses will have a different DIN for each format.

7 Available at <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/fact-sheets/drug-identification-number.html>.

available on the market or cancelled. We gathered all records in this database for human prescription drug products as of December 31, 2017.

Methodology for Compiling Results

We combined shortage data from both the original and current databases into a single dataset; we identified duplicate shortages by DIN and start date and counted them only once. Since the outcome was yet to be determined for the most recent shortages, we selected a three-year period – April 1, 2013 through March 31, 2016 – during which the original database operated, for a detailed analysis of dose, formulation, DIN, duration of shortage and shortage outcome. These data were extracted between March 24, 2016, and July 7, 2016. In addition, to characterize the diseases affected, we added the Anatomical Therapeutic Chemical (ATC) code and name for each drug based on the World Health Organization (WHO) ATC/Defined Daily Dose (DDD) index. These numbers had not been included at the original website.

We calculated the duration of each shortage by subtracting the estimated resupply date (or discontinuation date), if provided, from the start date. We were able to calculate shortage durations for 1,716 of the 2,616 shortages reported in the analysis period. To estimate the proportion of all drugs available that were affected by shortages, we gathered the number of active (marketed) prescription drugs for humans listed in the Health Canada DPD in each year of the analysis period, and calculated how that number changed through time. These numbers became a denominator for expressing yearly shortages as a proportion of available drugs.

Finally, we determined whether drug products in the analysis period were innovator or generic products. We also used the following heuristic to

determine innovator/generic status across all drug products in the DPD: we assumed that innovator drug products are introduced before generic drug products with similar active ingredients; therefore, in each group of active ingredients, the manufacturer with the first approved drug product was the innovator and all its drug products in the group were marked as such, with all other drug products marked as generic.⁸

RESULTS

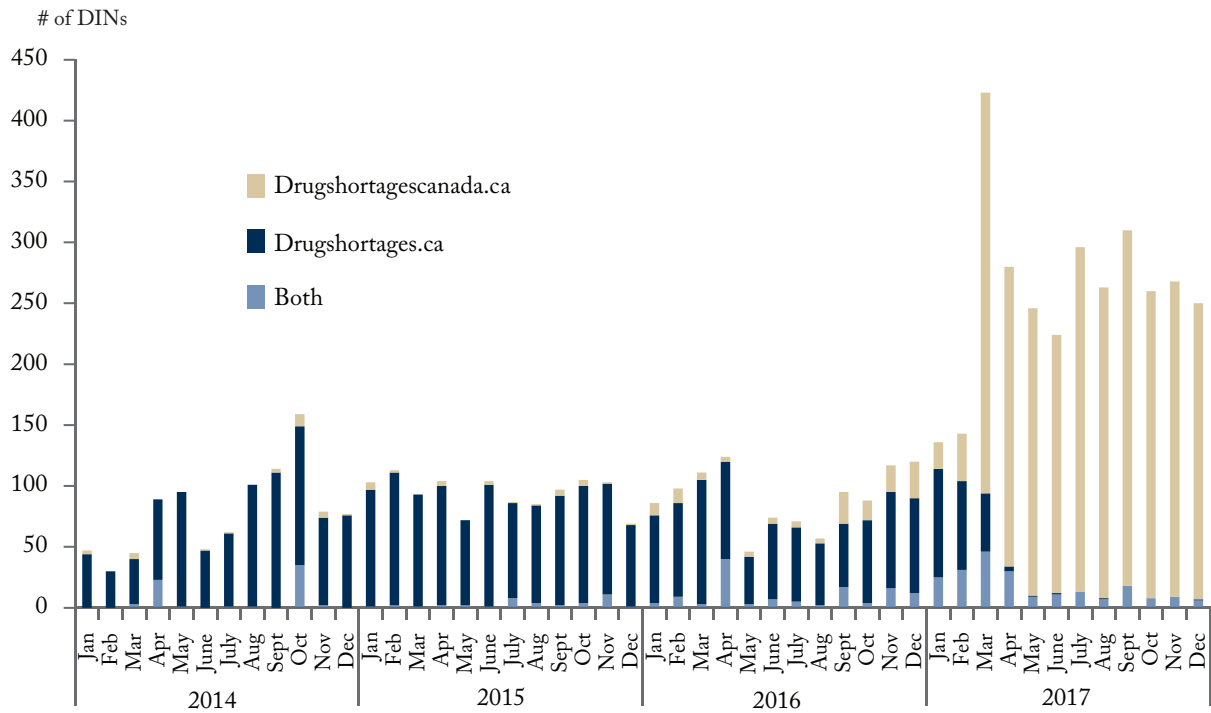
Figure 1 displays the total of 3,733 shortages listed in the database by year-end 2017. The apparent surge in reporting in March 2017 might be owing to the capture of persistent shortages from the original site and the simultaneous application of the broader definition and mandatory reporting. Most shortages (40 to 80 percent) reported in each year were eventually resolved (Figure 2).

During the period selected for detailed examination – April 1, 2013, to March 31, 2016 – 2,616 shortages were reported: 1,595 oral; 753 intravenous; 268 other. These shortages concerned at least 1,250 different products (by DIN number). In 1,716 of the reported shortages, duration was measureable. The median shortage duration was 59 days ($\sigma = 161$ days), with 120 of those shortages ending in discontinuations after a median duration of 40 days ($\sigma = 77$ days) (Tables 1 and 2). More than half the shortages owing to discontinuation were announced on the day of discontinuation – insufficient notice for clinicians to implement mitigation strategies. Only 15 discontinuations were announced in advance (the range was 1 day to 414 days).

The majority (77 percent) of drug shortages involve generic drugs, although a significant proportion (23 percent) also affected innovator drugs (Figure 3). These figures correspond to

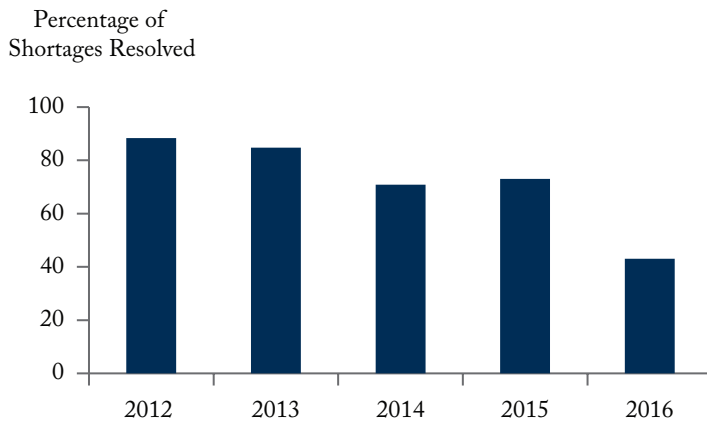
⁸ Source code for some of our analysis can be found at <https://github.com/pipitone/drug-shortages>.

Figure 1: Drug Shortages per Month, Canada, 2012–17



Sources: www.drugshortages.ca, launched in 2012; and <https://www.drugshortagescanada.ca>, launched in March 2017.

Figure 2: Percentage of Drug Shortages Resolved in Each Year, Canada, 2012–16



Source: www.drugshortages.ca, launched in 2012.

Table 1: Duration of Drug Shortages by Year, Canada, 2013–16

Year	Number	Mean	Standard Deviation	Median	Interquartile Range	Minimum	Maximum
2013*	189	94.7	127.5	62	81	0	820
2014	474	186.3	237.4	69	222	0	910
2015	814	102.1	112.2	59	108	0	649
2016**	239	80.6	81.7	53	84	0	414
Overall	1,716	121.6	160.8	59	108	0	910

* April 1–December 31. ** January 1–March 31.
Source: www.drugshortages.ca, launched in 2012.

Table 2: Duration of Shortages before Discontinuation of Drugs, Canada, 2013–16

Year	Number	Mean	Standard Deviation	Median	Interquartile Range	Minimum	Maximum
2013*	15	93.7	98.1	40	62	6	434
2014	22	76.5	98.4	47	66	0	366
2015	65	50.7	67.9	27	55	0	242
2016**	18	43.8	49.4	25.5	59	4	139
Overall	120	59.7	77.2	40	62	0	434

* April 1–December 31. ** January 1–March 31.
Source: www.drugshortages.ca, launched in 2012.

the relative prescription volume of generic and innovator drugs. The 20 companies, both generic and innovator, experiencing the greatest number of shortages for either oral or injectable medications are listed in Tables 3 and 4. For oral shortages, 10 companies made up 78 percent of all shortages reported; 20 companies made up 90 percent (Table 3). For injectable products, 10 companies made up

82 percent of all shortages reported; 20 companies made up 92 percent (Table 4).

Many drugs went into short supply on multiple occasions – up to nine times. Tables A1 and A2 in the [online appendix](#) present the 50 most frequently repeated drug shortages for various formats of oral and injectable drugs, affecting 35 and 40 active pharmaceutical ingredients, respectively. Sometimes

Table 3: Twenty Generic+ and Innovator++ Companies Reporting 90 percent of 1,595 “Oral” Drug Shortages, Canada, 2013–16

Company Name	Number of Products (DIN)	Number of Shortages	% of Total Shortages
Teva Canada Limited+	223	323	20.25
Apotex Inc.+	220	241	15.11
Pharmascience Inc.+	103	134	8.40
Pfizer Canada Inc.++	77	103	6.46
Mylan Pharmaceuticals ULC+	91	99	6.21
Valeant Canada+	87	90	5.64
Sanis Health Inc.+	74	81	5.08
GlaxoSmithKline Inc.++	32	70	4.39
Sandoz Canada Inc.+	56	70	4.39
JAMP Pharma Corp.+	26	27	1.69
AstraZeneca Canada Inc.++	19	26	1.63
Laboratoire Riva Inc.+	25	26	1.63
Laboratoires Trianon Inc.+	23	23	1.44
Novartis Canada Inc.++	17	22	1.38
Paladin Labs Inc.+	19	22	1.38
Sanofi Canada++	17	20	1.25
BGP Pharma ULC+	16	17	1.07
Bristol-Myers Squibb Canada++	13	15	0.94
Merck Canada Inc.++	9	15	0.94
Total	1,147	1,424	89.28

Note: Period covered is April 1, 2013–March 31, 2016.

Source: www.drugshortages.ca, launched in 2012.

all doses of the same drug were unavailable at the same time, preventing the doubling up or division of other dose formats to compensate for a shortage. In these cases, pharmacists and physicians were forced to look for alternative treatments with different medications or even medications from a different therapeutic class of drugs that might suit the intended clinical indication and patient condition.

As for therapeutic class, the most significant repeated oral drug shortages concerned medications

for cardiovascular, nervous system and infectious use indications. For injectable drugs, most shortages concerned treatment for infectious, electrolytic-metabolic, gastrointestinal, cardiovascular and nervous system use indications (Figure 4, Tables A3 and A4 in the online appendix). Shortages of antineoplastic drugs were not as numerous, although many medications in short supply that are not classified as oncology drugs are applied to the side effects of cancer treatment. Oncology shortages are especially difficult to manage, as fewer

Table 4: Twenty Generic+ and Innovator++ Companies Reporting 90 percent of 738 “Injectable” Drug Shortages, Canada, 2013–16

Company Name	Number of Products (DIN)	Number of Shortages	% of Total Shortages
Hospira Healthcare Corporation+	96	192	26.02
Sandoz Canada Inc.+	118	174	23.58
Teva Canada Limited+	35	61	8.27
Pfizer Canada Inc.++	34	47	6.37
Omega Laboratories Ltd.+	27	37	5.01
Fresenius Kabi+	20	31	4.20
Baxter Corporation++	23	24	3.25
GlaxoSmithKline Inc.++	11	21	2.85
Apotex Inc.+	11	13	1.76
Aspen Pharma Trading Ltd+	5	13	1.76
Mylan Pharmaceuticals ULC+	11	11	1.49
Sanofi Canada++	7	9	1.22
Bristol-Myers Squibb Canada++	6	8	1.08
Hoffmann-La Roche Limited++	8	8	1.08
SteriMax Inc+	5	8	1.08
Merck Canada Inc.++	3	7	0.95
Total	420	664	89.97

Note: Period covered is April 1, 2013–March 31, 2016.
Source: www.drugshortages.ca, launched in 2012.

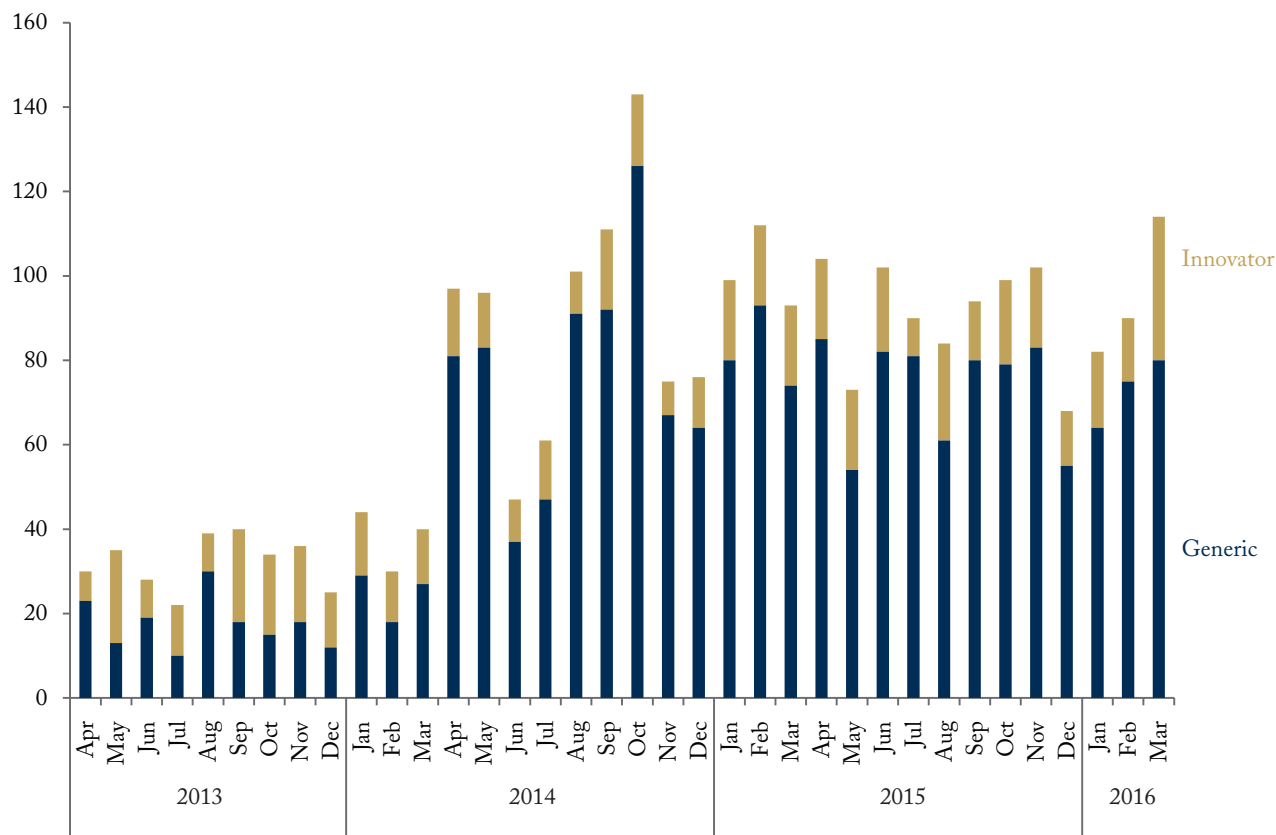
therapeutic alternatives usually are available. Using only the shortages reported since March 2017, we noted a similar distribution of therapeutic class (Figure 5). It is important to note, however, that drugs with the most frequently reported shortages (such as ramipril) might not have been truly absent at any point, because the website gave no indication of whether or not it was “medically necessary” with or without other suppliers.

Discontinuations were most frequent for oral, generic products, rather than for injectable or innovator medicines, and they were especially numerous in 2014 (Figure 6). Again, using ATC codes, discontinuations most often affected oral

treatments for nervous system and cardiovascular use indications, while discontinuations of injectable medications were most frequent for infectious use indications (Figure 7).

A more finely grained presentation of the types of discontinued products is presented in online Tables A5 and A6. The generic or innovator drug companies that reported the most discontinuations of oral and injectable drugs are presented in Tables in appendix A7 and A8, respectively. Some manufacturing companies license and make available many products, others only a few (Figure 8). These data remind us that, given a relatively equal distribution of drug-shortage causes, the companies having many

Figure 3: Shortages of Generic or Innovator Drug Products over a Three-Year Period, Canada, 2013–16



Note: Period covered is April 1, 2013–March 31, 2016.

Source: www.drugshortages.ca, launched in 2012.

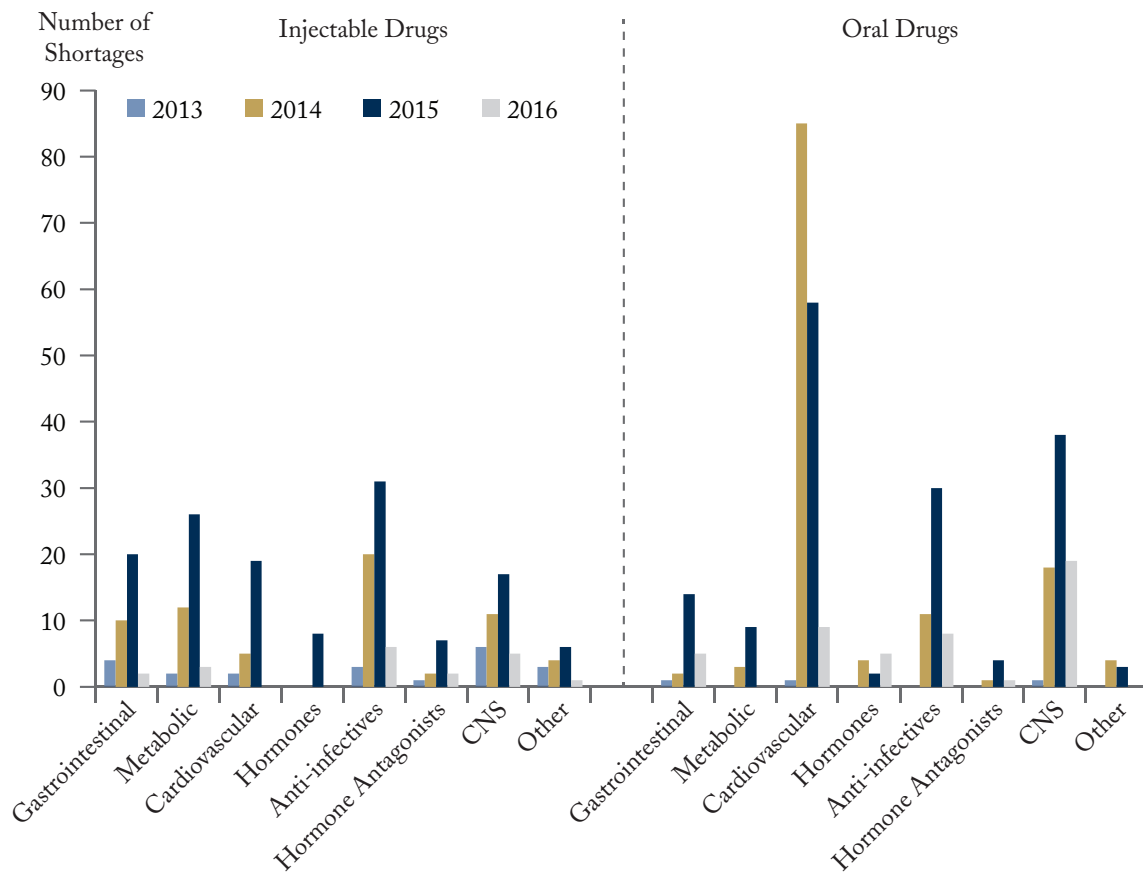
products are likely to experience more shortages. Therefore, Figure 9 expresses the percentage of shortages for the top 10 manufacturers as a ratio of their marketed products. Those companies appearing above the line (which represents a ratio of 1) have experienced more reported shortages than anticipated based on their market share.

Health Canada's DPD reveals that, for the years since 2012, approximately 7,000 to 8,000 prescription drug products (10,000–12,000 including over-the-counter products) are active, meaning that they are licensed and marketed. We analyzed the distribution of generic versus innovator products by the year of availability since 1970 to show that, as expected from an

increase in patent expirations, generic products have predominated since the mid-1990s, with an additional increase in proportion since 2009; the number of innovator products predominated until the mid-1990s, and has remained relatively stable since that time (Figure 10). Using these data in Figure 10 as a denominator for the three years of our study, approximately 10 to 11 percent of all active prescription drugs were in short supply at some point (Table 5).

For a snapshot of the situation on a single day, on March 24, 2016, the website listed 760 ongoing shortages with start dates ranging from March 23, 2012, to December 31, 2016 (an advanced announcement), and duration ranging from 2 days

Figure 4: Top 50 Repeated Shortages of Injectable and Oral Drugs, Canada, 2013–16, Using ATC Code



Note: Period covered is April 1, 2013–March 31, 2016.
Source: www.drugshortages.ca, launched in 2012.

Table 5: Proportion of Active Products Affected by Shortages, Canada, 2013–16

Year	Number of DINs Affected by Shortages	Number of Active Products (by DIN)*	Percentage
2013	263	7,320	3.6
2014	839	7,873	10.7
2015	922	8,270	11.2
2016	274	8,559	3.2

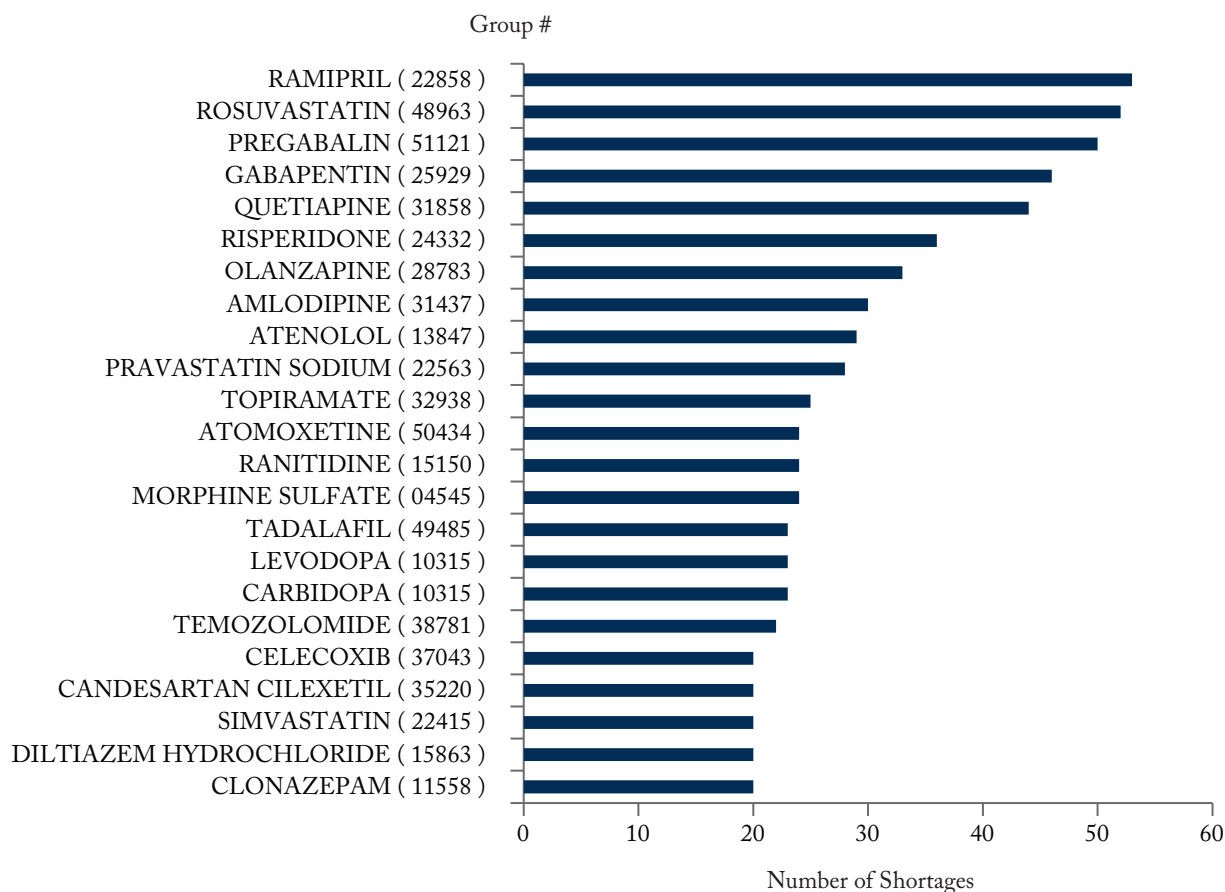
Sources: www.drugshortages.ca, launched in 2012; and Health Canada, Drug Products Database, available online at <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php>, accessed March 21, 2017.

to 1,462 days. Only 8 (1 percent) of the 760 had been announced in advance (range, 2 to 414 days). At least 396 (52 percent) had been announced on the first day of the shortage. On that day, 161 shortages had been “resolved” in the eight previous weeks since January 25, 2016.

Gaps in Knowledge and Causes

Clinicians and pharmacists had long complained about the limitations of the original drug shortage reporting site: some shortages were

Figure 5: Top 21 Shortages by Ingredient (and Group Number), Canada, March–December 2017



Sources: Health Canada, Drug Products Database, available online at <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php> 2012-2017; and <https://www.drugshortagescanada.ca>, launched in March 2017.

ignored, possibly due to confusion about the definitions, and few were announced in advance. Because uptake of the site was slow during the era of voluntary reporting, the earliest data did not reflect the situation with accuracy. Some shortages were likely deleted, because the site remained open to editing. Deletions might have been accidental when an old resolved entry was used to create a new entry by altering the start date. In the meantime, some manufacturers and some provinces began to create their own reporting sites due to the lack of a clear leadership role by Health Canada. The

apparent increase in the frequency of shortages on the new website might reflect increased reporting and use of the database owing to the effect of mandatory reporting and the broader definition of shortages, rather than an actual change in the number of shortages. Nevertheless, it is important to emphasize that these two sites are the only publicly available sources covering the period from 2010 to 2017. At the very least, in combination, they provide a baseline *minimum* for the number of shortages, and they reflect the gradual acceptance of such a site by MAHs over time.

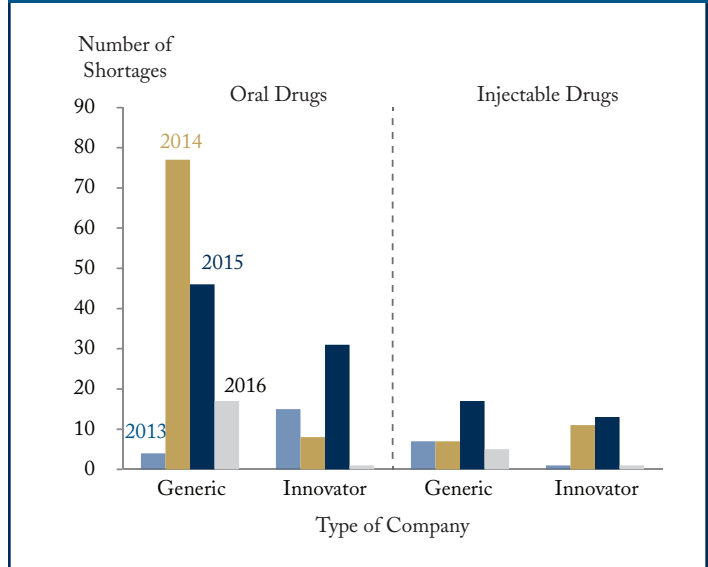
Individual drug shortage records were frequently updated, most often to extend the “estimated resupply date.” The original website did not retain the date of first announcement or start date, but replaced it with the date of the “last update.” Consequently, the duration and number of shortages in our study might be falsely low. From a clinical perspective, it is important and desirable that suppliers be transparent about the actual resupply date, to allow for the proper mitigation strategies to be implemented. A significant number of shortages in our study, however, was caused by the discontinuation of products, sometimes with little or no notice at all. These withdrawals also skewed downward the apparent duration of all shortages, because they appear to have generated a shortage of only a few days when in fact the product might never have become available.

The shortages appear to have affected at least 10 percent of all active drugs available in Canada (Table 5), but it is not known what proportion they affected of drugs actually prescribed. In addition, this information should be tempered by regional differences, since provincial formularies do not always include active drug products from the same suppliers. Furthermore, DINs are more numerous than are active pharmaceutical ingredients, since the same ingredient in the same dose made by two manufacturers will have two different DINs; therefore, more finely grained reporting is needed to determine the medical necessity of DINs in short supply.

The MAHs most affected by shortages were those that had the most drugs actively available in Canada, suggesting that shortages might have occurred evenly across all drug products. These companies also might have been more diligent than others in reporting shortages as they occur.

The precise causes of Canadian drug shortages are not known. The original drug shortages website did not require tracking of causes, and a voluntary reporting field for the cause of each shortage was frequently ignored. The new website demands that a cause be supplied. “Manufacturing problems” – a

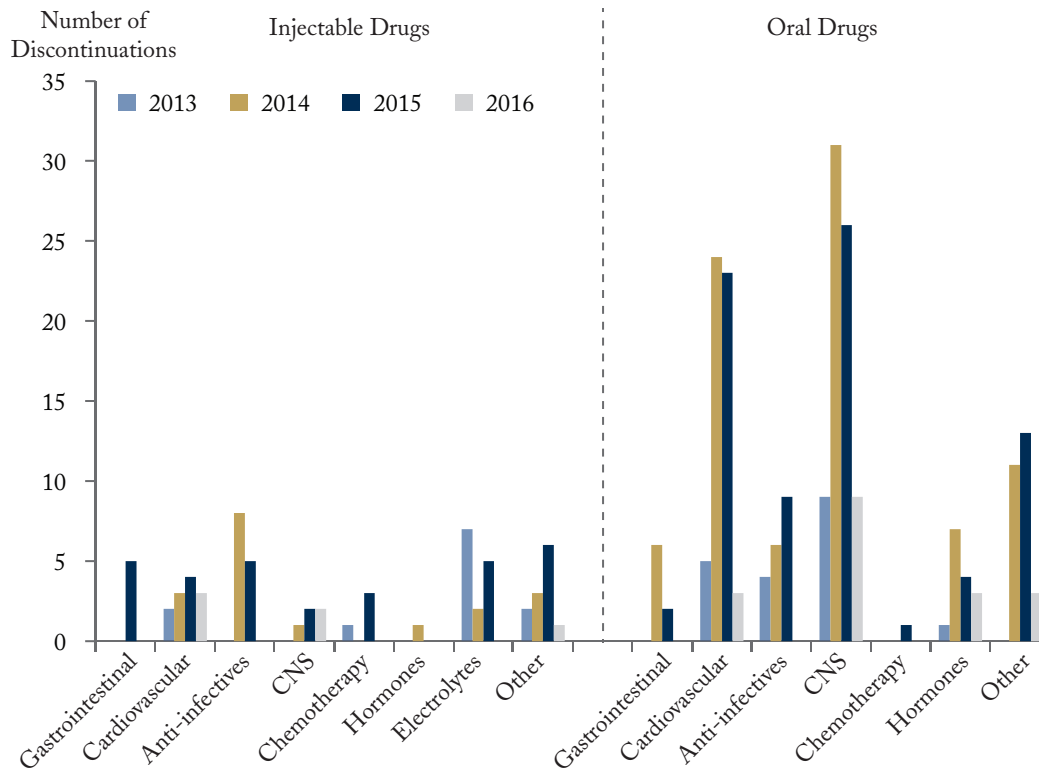
Figure 6: Reported Discontinuations by Generic or Innovator Companies, Canada, 2013–16



Note: Period covered is April 1, 2013–March 31, 2016.
Source: www.drugshortages.ca, launched in 2012.

commonly cited but vague reason for shortages – can occur when an inspection uncovers a finding of concern, such as potential for contamination of sterile products, resulting in the closing of a production line until the problem is resolved. Although, in the United States, the FDA has established several foreign inspection offices in response to the increasing supply of imported pharmaceutical products, Health Canada relies predominantly on a process of documentation review and mutual recognition agreements. Regulators often take action against unreliable manufacturers that fail to meet quality-control requirements essential to product safety. Industry and the US Congress have both blamed overzealous FDA inspections for some shortages (United States 2012a). Another commonly reported cause is “shortage of raw materials”; however, although different arrangements might prevail about origin, supplier, access and approvals of raw materials, the same, generally recognized as safe raw materials are used to produce both generic and innovator drugs. Some of the ambiguity in reporting causes might

Figure 7: Reported Injectable and Oral Drug Discontinuations, Canada, 2013–16



Note: Period covered is April 1, 2013–March 31, 2016.
Source: www.drugshortages.ca, launched in 2012.

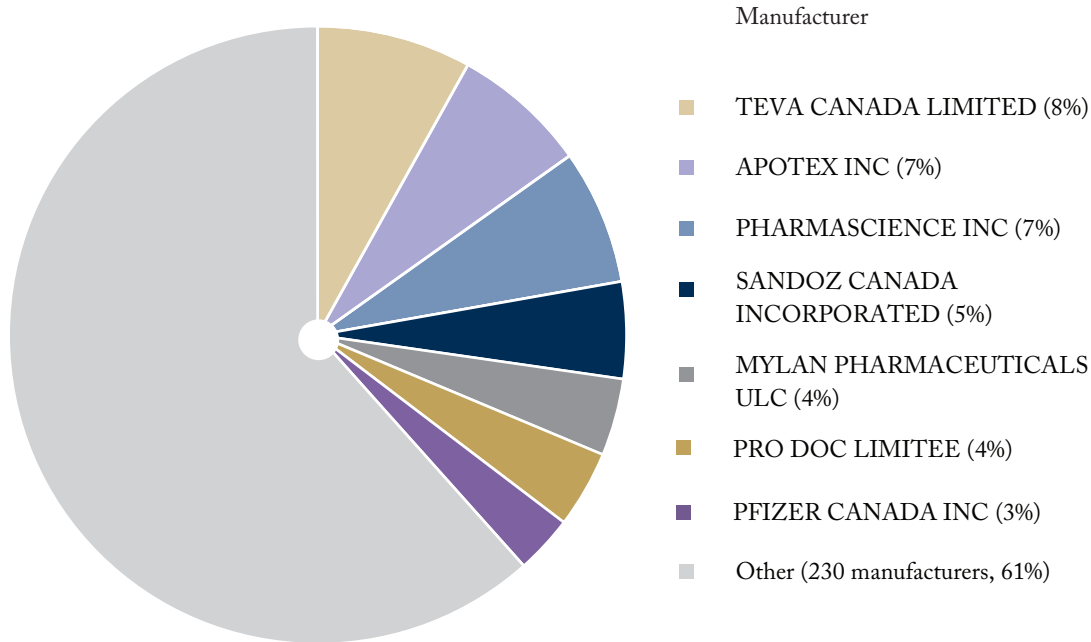
be owing to the website design itself, which allows only for certain etiological “choices.”

Market factors also play a role. Some argue that generic drug prices are too low, causing their makers to abandon them; others claim they are too high. Several observers point to the practices of the large US GPOs, which have created a monopsony in the market, creating shortages for those entities outside their client base (Sethi 2009). Others claim that increased global demand and new markets in developing nations are putting pressure on availability; however, generic manufacturers extract higher margins from sales in Canada than in developing nations, and should have an incentive to maintain market supply.

DRUG SHORTAGES: AN INTERNATIONAL PROBLEM

Drug shortages are a global problem, although their manifestations vary among countries. Most countries do not measure them, but media sources report on individual crises as they emerge, detailing their effects on pressing health problems. Based on the reports at our information website, Europe, North America and China can be characterized by shortages of drugs for cancer, arthritis, cardiovascular or hormonal diseases, and epilepsy; Australia and New Zealand have suffered shortages of antivirals, antibiotics and cardiac drugs. Although the causes might differ, reports from India and

Figure 8: Market Share by Major Drugs Producer, Canada, 2013–16



Note: Period covered is April 1, 2013–March 31, 2016.

Source: Health Canada, Drug Products Database, available online at <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php>.

various African nations emphasize shortages of medications for malaria, tuberculosis and HIV-AIDS (Duffin 2011-2018). In other words, the drugs that are most often in short supply are those that are most in demand.

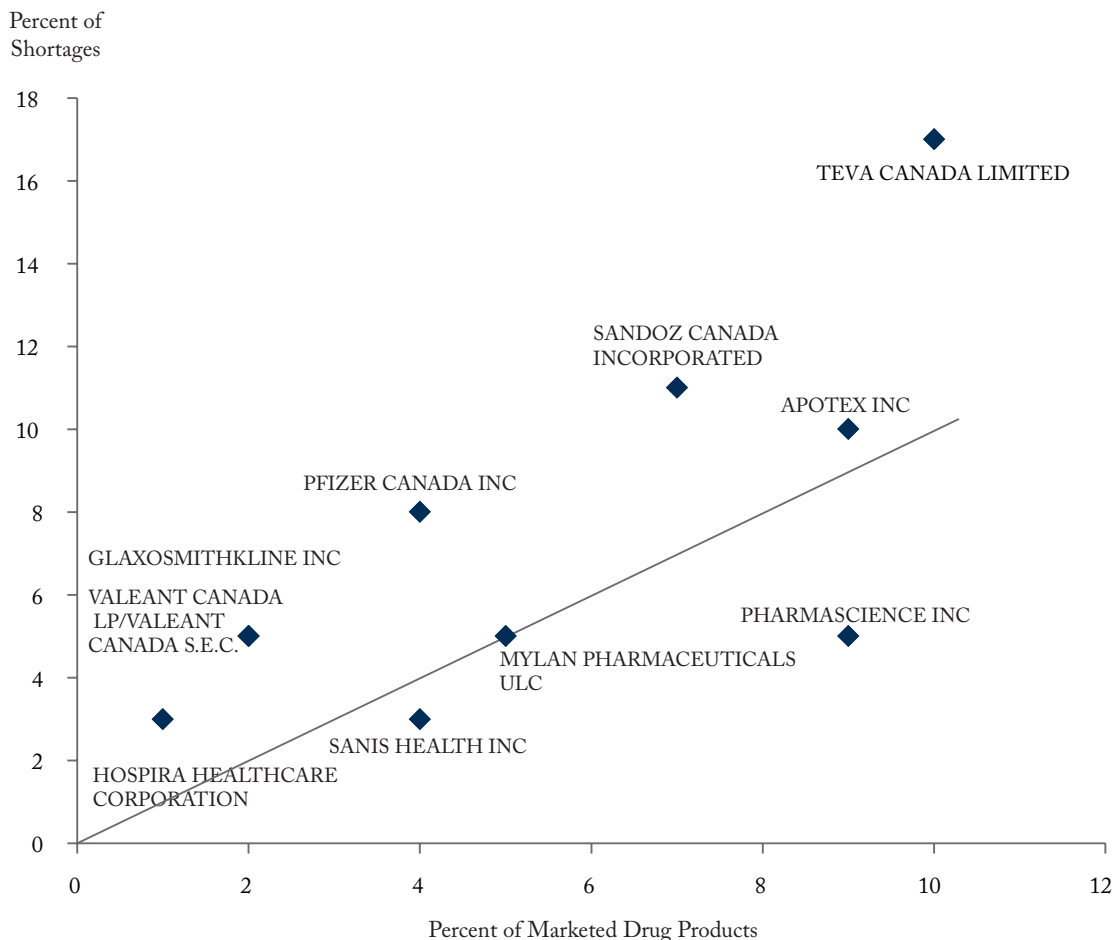
Policies to Prevent or Respond to Shortages

Policies to prevent shortages have often been invoked in haste in response to each crisis. Increased funds and the scramble to find alternative suppliers characterize most of the responses from around the world.

In the United States, mandatory reporting of “medically necessary” products became compulsory by an executive order in October 2011. Mandatory reporting gives pharmacists and healthcare

providers time to mobilize in each crisis, but it does not address the causes or help diagnose the problem from a policy perspective. Measurement also became mandatory in the United States, and in early 2014 the FDA released its first required annual report on the status of US shortages, listing both new and continuing shortages, identifying drugs and diseases concerned and comparing results to previous years (United States 2014a). The most recent report was tabled in May 2017 (United States 2017). The US GAO has also been studying and measuring the problem (United States 2014b, 2016). These annual measurements indicate that shortages of injectable drugs predominate in the United States. Recent reports from both agencies suggest that the number of new shortages might be declining, while continuing shortages are not. These

Figure 9: Top 10 Drugs Producers by Number of Shortages, Canada, 2013–16



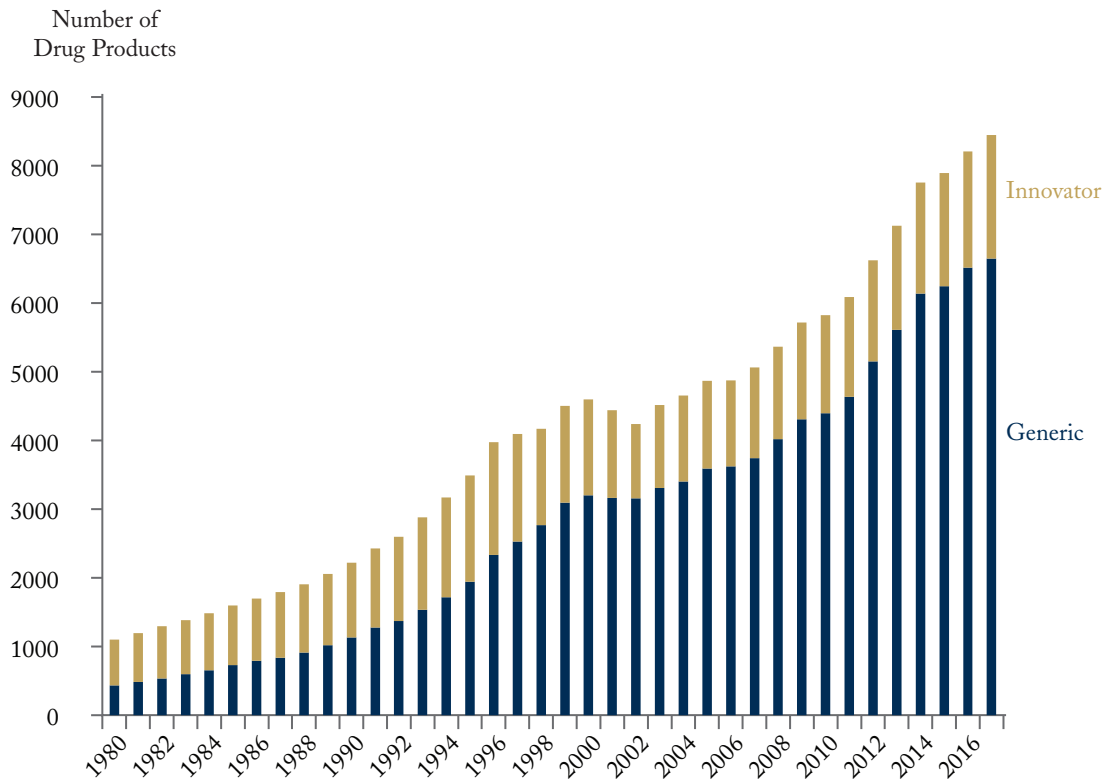
Note: Period covered is April 1, 2013–March 31, 2016.
 Sources: Health Canada, Drug Products Database, available online at <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php>; and <https://www.drugshortagescanada.ca>, launched in March 2017.

measurement reports are used to mitigate shortages by identifying substitutes and alternate sources; they are also used through time to assess the effects of policies designed to help and prevent shortages. In the Netherlands, similarly, after a shortage of levothyroxine in 2017, a notification centre for mandatory notification and measurement was set

up to track shortages and facilitate the search for alternative medications.

Other mitigating solutions used in the United States include fast-tracking approvals for new substitutes and older alternate sources. Along these lines, in March 2016, the FDA offered to speed up applications to manufacture drugs that

Figure 10: Drug Products (DINs) Available Each Year, Canada, 1970–2017



Source: Health Canada, Drug Products Database, available online at <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php>, accessed October 17, 2017.

currently have only one supplier (Brennan 2016; Morris 2016). Health Canada should consider this policy to deal with shortages of selected injectables, especially by allowing accelerated abbreviated new drug submissions for medically necessary products through its existing priority review procedure, which is currently available only for new drug submissions (Canada 2007). Fast-tracking or accelerated review might prevent some shortages, but it can result in danger and/or legal action, as, for example, in the US meningitis

outbreak of 2012 that affected more than 800 people, with 76 deaths, and led to a jail term for a pharmacist (Bidgood 2017). The situation emerged when a shortage provoked a decision to use a substitute from a compounding pharmacy that was operating under conditions that did not meet Good Manufacturing Practice requirements. Encouraging more competition between manufacturers and incentivizing development of generic drugs, especially when there is only one source, is the purpose of a bipartisan bill introduced in the US

Congress by senators Susan M. Collins (R) and Claire McCaskill (D) in early 2017.⁹ Read twice, currently under study by the Committee on Health, Education, Labor, and Pensions, and supported by GPOs (Ebert 2017), it proposes to combat shortages through enhanced competition.

The United States has also discussed enforcing the “duty-to-supply clause” in licensing contracts. So far, however, this strategy has not worked: the US Supreme Court has refused to hear arguments that companies have a duty to supply, made by people allegedly injured as a result of drug shortages, for example, Jennifer Lacognata who went blind and the widow of Dr. William Schubert who died of Fabry’s disease (Thomas 2012; US District Court 2013). This result affirms the idea that “medicine manufacturers have no legal duty to continue selling medicines when they want to stop,” and that a duty to keep selling “compete[s] far too fundamentally with the essential premise of the American free enterprise system” (Janssen 2014, 392). Duty-to-supply clauses are rarely enforced for other manufacturing products, and this strategy invites discussion of what, if anything, is different about pharmaceutical products. The Access to Medicines program aimed at developing nations has defined the duty to supply as an aspect of human rights responsibility, which by extension could apply anywhere (Droppert and Bennett 2015; Lee and Hunt 2012).

Bulk purchasing is used in many situations to lower drug prices and supplement stocks, but it is not clear what long-term effect it has on drug shortages, since lower prices have been cited as a cause of shortages and discontinuations. The practice of tendering used in these initiatives could

lead to shortages by discouraging manufacturers, resulting in single-source suppliers.¹⁰

In terms of prevention, an Essential Medicines List (EML) is regarded as crucial. According to the WHO, 117 countries, including several developed nations, maintain an EML. A national commitment to maintaining and stocking drugs on such a list helps to guarantee and protect supply. EMLs have proved to curb drug shortages, or are expected to do so, in several nations, including New Zealand, Norway, Sweden and, most recently, Gambia (Cham 2017; Eom, Grootendorst, and Duffin 2016).

WHAT TO DO?

Analysis and reports by Canada’s Multi-Stakeholder Steering Committee on Drug Shortages, of which Health Canada is a member, are available online. Community and hospital pharmacists now collaborate to reasonably good effect in helping clients find their medications or good substitutes. But we still have more to learn from the differences revealed by measurement between shortages in Canada and those elsewhere and from policies used in other nations. Uncovering those differences becomes all the more difficult in the absence of an internationally accepted definition of shortages.

Proactive Responses to Shortages

Managing Shortages

Measure shortages and heed early warning signs: Our results for Canada corroborate and extend the findings of Rinaldi et al. (2017), who base their analysis on a different source that ends in 2014. Like US shortages, the majority of

9 See “Making Pharmaceuticals More Competitive Act, S.1115,” available online at <https://www.congress.gov/bill/115th-congress/senate-bill/1115/text>.

10 For some hospital-specific drugs, contracts are awarded to more than one supplier to ensure an alternative supply. <https://portal.healthprocanada.com/web/healthpro-public/newsfeed-view?assetId=1003067>.

Canadian shortages involve generic drugs; however, innovator shortages also occur, possibly more frequently than in the United States. Industry representatives suggest that they happen when a generic shortage provokes a temporary run on an innovator substitute for which marketers had not been prepared, with the generic industry tending to take the “blame.”¹¹ Our study shows, however, that, unlike in the United States, the majority of Canadian shortages are of oral products, with a sizable minority involving injectable drugs. The differences have not been addressed in current policies. In addition to counting the number of shortages, their duration should also be tracked. Furthermore, apparent differences between the two countries might be influenced by varying definitions of shortages and the extent to which reporting includes “all shortages” or only those that are “medically necessary.”

Make advance reporting of shortages mandatory: Advance reporting of shortages, used with increasing reliability in Canada since March 2017, would be helpful, saving time for doctors, pharmacists and patients in preparing for an eventual shortage by providing time to identify substitutes and alternate sources. It is unclear how strongly this policy has been or should be enforced and what definition of shortages should be used.

Develop ethical decision-making tools for allocating scarce resources: Bioethicists have hosted several conferences to develop guidelines on how such decisions should be made – for example, choosing to supply an analgesic to a dying elderly person or a child with cancer; pediatric guidelines appeared in early 2016 (see Unguru et al 2016).

Add information about alternatives and substitutes and their availability to the reporting website:

Currently prescribers have limited access to the information needed to make appropriate decisions. A recent study suggested that rates of adverse events might differ between brand-name and selected generic cardiovascular products. Repeat drug shortages may further compound this potential problem by exposing patients to frequent intergeneric switching (Leclerc et al., 2017).

Fast-track approval of substitutes and “sole-source” or “single supplier” products: The approvals process could be enhanced by eliminating hurdles for industry and by harmonizing regulations.

Encourage the development of new manufacturing technologies to introduce flexibility and efficiencies into the supply system in answer to increased demand; see, for example, the Massachusetts Institute of Technology’s portable machine, announced in April 2016, or the Canadian-owned VanRx Aseptic Workcells.¹²

Preventing Shortages

Notwithstanding its merits, mandatory reporting can do nothing to prevent shortages because it does not address the causes, which are unpredictable and vary from case to case. Learning more about unknown causes would help prevent shortages. Identifying variation between nations through local needs and supply chains could be one step toward that goal. Other steps could include the following:

An Essential Medicines List and a pharmacare plan, both proposed for Canada, could encompass those drugs that are most frequently used and help

11 Paul Lucas, at the time chairman of the board of Rx&D Canada (now Innovative Medicines Canada), personal communication, July 31, 2014; see also Russell Williams, President of Rx&D Canada to the Standing Committee on Health, March 27, 2012, available online at <https://openparliament.ca/committees/health/41-1/36/russell-williams-1/only/>.

12 See Massachusetts Institute of Technology, “Portable pharma manufacturing system produces drugs on demand,” Pharmpro, 1 April 2016, available online at <https://www.pharmpro.com/news/2016/04/portable-pharma-manufacturing-system-produces-drugs-demand>; and Vanrx Pharmsystems Inc. <https://vanrx.com/company>.

prevent supply shortages through a commitment to maintain stocks (Eom, Grootendorst, and Duffin 2016; Morgan et al. 2015, 2017). Although a national pharmacare plan would not prevent shortages, coupled with right supply arrangements, it could prove more effective in identifying and managing them as they occur.

Further research to identify the “medical necessity” of drugs affected by shortages: This step would be helpful in a number of ways. The United States does not have an EML, but it determines that a drug is medically necessary if it is used “to treat or prevent a serious disease or medical condition, for which there is no other adequately available product that is judged by medical staff to be an appropriate substitute” (United States 2012b, 12). Such an exercise would determine what, if any, alternative drugs might substitute for the products and ingredients with unique active pharmaceutical ingredients that have disappeared in the short term, as would be the case with a single supplier. But it could also contribute to identifying products that belong on an eventual Essential Medicines list, and help industry by indicating marketing strategies and supply chain arrangements that work and those that do not. At the very least, it could help with the ambiguity over definitions that lead to overreporting.

Track and document manufacturing problems: Improved reporting by Health Canada of the most frequent quality issues identified for all manufacturers, could generate information about how to avoid manufacturing problems, since these are the most frequently cited causes of shortages by industry. Since 2015, Health Canada has considerably improved its efforts to provide more transparent results of its regulatory compliance and enforcement efforts in both domestic and foreign inspections against good manufacturing practice requirements for safety and quality. In its Annual Inspection Summary Reports, Health Canada cites the most commonly observed quality issues (Canada 2017). Additionally, in the Drug and Health Product

Inspections Database, Health Canada publishes the results of the inspections it conducts at domestic and foreign facilities (Canada 2016).

Although intended to improve access to the public, the inspection database is not user-friendly and contains approximately 6,500 entries going back to January 2012, which cannot be searched easily by non-experts. Close to 80 percent of prescription drugs sold in Canada are imported, yet Health Canada directly inspects only about 1 percent of foreign manufacturing sites, with the remainder subject to a paper review of inspection activities conducted by other regulatory agencies. Consequently, there should be more open disclosure of how this process works and what audit measures are taken to ensure that Canadians are appropriately protected from defective products. There should also be a cross-analysis of manufacturers with repeated shortages attributed to manufacturing problems and the actual results of the manufacturing inspections conducted during the same period.

Study and control market forces and the appropriate price for generic drugs: Some argue that prices are too low to make the drugs profitable; some argue that generic prices soar inappropriately to take advantage of shortages. This practice does not take place in Canada, as the price in the retail sector is controlled through the tiered-pricing framework, but selected shortages of different dose strengths of the same medication have been reported and this may result in increasing the cost of care (Grant 2018 b). In the institutional setting, however, generic manufacturers can charge high prices for medicines that are in short supply from a contract supplier, as the GPO tendering process sets the price for the product awarded the tender, but not for alternatives, which are often not listed on provincial formularies. Nevertheless, the generic industry is not responsible for the higher prices of innovator substitutes or of products supplied from other countries, all of which lead to increased costs for the healthcare system. Bulk purchasing has become popular to generate cost savings. In

Canada, it was attempted with some fanfare by the Council of the Federation in 2012 (Taber 2012), and most recently through promises by the pan-Canadian Pharmaceutical Alliance, industry, and the federal and provincial governments – not without controversy – to lower prices for generics by April 2018 (Grant 2018a; Picard 2017). Bulk purchasing, however, together with the effect of large US GPOs, might drive the cost of drugs so low that companies stop making them.

Contract restructuring, through which buyers could include penalties for shortages, might mitigate this problem. Current funding for the drug review and approval process in Canada comes primarily from taxpayers, and most of the time several applications are submitted for the same product by several different generic suppliers aiming to capture market share. A related issue is the barrier (to market access) for generic suppliers to obtain a Notice of Compliance. They must apply for an Abbreviated New Drug Submission, with review fees in the range of \$50,000, subject to remission if the actual gross revenue is less than anticipated (Canada 2015). In other words, if obtaining an MAH licence is inexpensive, one might speculate that there is a lesser incentive to recover an investment by ensuring an adequate market supply. MAHs might be “taking positions” without “exercising them fully,” an effect that could be more at play for oral products than for injectable ones because the ability to manufacture the latter is in itself an important barrier. The overall pharmaceutical product supply chain, from licensing to listing to reimbursement by provincial formularies, should become much more transparent.

Require manufacturers to respect the “duty-to-supply” clause of licences: Contractual obligations for drug delivery might lack appropriate risk mitigation to ensure supply, in part because of the way contracts are structured. The focus might be too much on a manufacturer’s ability to supply a product at a given price and less on its capacity to do so at any given time. This scenario is directly related to the “capacity market” concept in

electricity markets: to ensure a reliable electricity supply, a capacity market pays electricity generators for their ability to generate, not just for the energy they produce. Capacity markets explicitly recognize that additional value resides in the ability to provide a greater volume of products. Accordingly, there could be two aspects for contracting drug purchases: one based on the drugs that producers create and another for the capacity of drugs that they could produce at any given time.

Create a nationally owned pharmaceutical manufacturing entity: Canada used to host a thriving pharmaceutical manufacturing industry. Since 1960, however, the number of companies owned or based in Canada has declined sharply, with a decline in all manufacturing and a rising trade deficit in pharmaceuticals (Lexchin 2005). American scholars have recently made a similar suggestion (Liljenquist et al. 2018). Former College of Physicians and Surgeons of Ontario president George Miller agrees with the suggestion that Canada should encourage growth in a home-based generics industry (quoted in Duffin 2011–2018, esp. 2016). An important caveat to this approach is that it would require Canada’s current drug-purchasing approach to evolve by incorporating concepts of reliability of both supply and cost, which currently favours the commoditization of medicines and the centralization of global manufacturing.

Encourage more competition between manufacturers, and expedite approvals: With contract restructuring to include penalties for shortages, competition would focus not only on price, but also on reliability in supply. Current procurement practices and pricing policies have had the effect of gradually reducing the diversity of manufacturers of some molecules, thus placing these products at increased risk of shortages.

Encourage increased harmonization between the generic and innovator industries: Drug prices inevitably include the legal costs of defending and challenging patents.

Encourage greater transparency and patient engagement by requiring MAHs to reveal the source

of supply of each product in Health Canada's database; currently no such information appears in either the database or the product monograph. As Health Canada recently described, consumers are in a tough spot with medicines because all transactions are managed by health professionals (Health Canada 2018). But in these times of increasing patient-centred care, advocacy and agency, we suggest that patients (consumers) be notified by their pharmacist of the company that supplies their prescription products under shortage. Shortages might happen, but should not as a recurring matter. Patients who face repeated shortages from the same supplier could request that their pharmacist consider excluding that supplier as a source of their prescriptions, which would create bottom-up pressure for prescriptions to be filled by more reliable suppliers.

CONCLUSIONS

This *Commentary* represents the first attempt to measure and characterize persistent drug shortages in Canada, as expressed in Health Canada's original drug shortages database and in its successor.

Approximately 1,000 shortages have been reported annually, affecting 1,250 products during a recent three-year period. Indeed, the number of shortages appears to be increasing, although this apparent rise might be explained by growing pressure to adhere to the policy of mandatory notification, even if its enforcement is still lacking.

A sharp jump in the number of shortages was noted in the second quarter of 2014, for example, after technical changes at the website facilitated data entry, signifying better reporting compliance rather than an actual increase in shortages. The majority of shortages in Canada have been of generic products in oral format.

A stable supply of a diversity of medicines from a diversity of manufacturers is necessary to keep health care costs down, avoid expensive solutions to sudden emergencies and maintain access to medications for the entire population and for the 10 percent of Canadians who cannot afford their prescription drugs (Law et al. 2012). Measuring shortages on a regular basis would reveal important information about the nature and extent of the problem, and provide a baseline for assessing the effectiveness of policies created to manage and prevent it.

We hope that regular analysis of the drug shortage problem will generate insight into its possible causes. With Health Canada's improved website, it should be easier to undertake this kind of reporting in the future. We urge Health Canada to provide annual reports on the drug shortage problem in an effort to define it, explain it and, above all, solve it. We also urge the federal government to show leadership on the global stage by inviting nations to work together to understand the nature of drug shortages around the world. Only when the causes are identified can solutions be found.

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