



## Context

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While drug shortages are not uncommon,<sup>1,2</sup> their frequency and duration may be escalating.<sup>3</sup> Drug shortages are currently believed to be more prevalent in the generic drug market in Canada, than in the brand name market.<sup>4</sup>

Unanticipated and poorly communicated drug shortages and discontinuations in drug product lines may impact the delivery of patient care.<sup>2,3</sup> The effect on the delivery of health care services, particularly with regard to the administrative resources required to source alternative drug therapies, and the financial consequences of substitute therapies (which are often more expensive) are other areas of impact of drug shortages.<sup>2,3</sup>

The problems encountered by disruptions in drug supplies are often magnified by the absence of advanced warning from drug manufacturers. This is of particular concern when the affected drugs are sourced from single or primary suppliers.

Many factors can influence the occurrence and severity of drug shortages.<sup>5</sup> The most frequently cited reasons for shortages in the drug supply chain include issues relating to raw and bulk material suppliers, manufacturers, wholesalers, distributors, and regulatory bodies.<sup>3</sup>

Concern that drug shortages may continue during the coming years<sup>6</sup> underscores the need for strategies and procedures, at every level of the drug supply chain, to minimize disruptions to patient care.

## Objectives

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The purpose of this report is to provide information on the causes and impact of drug shortages in Canada. The following questions will be addressed:

- What are the main causes and the impact of drug shortages?
- What is the international drug shortage experience?
- What strategies can be implemented at various levels of the health care system to mitigate drug shortages?

## Findings

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The findings of this environmental scan are not intended to provide a comprehensive review of the topic. Results are based on a limited literature search and communication with key informants. This report is based on information gathered as of February 14, 2011.

The first section of this report will present information on general drug shortage issues in Canada. The second section will explore the international drug shortage issue with a specific focus on the United States (US), Europe, Australia and New Zealand. The third section of this report will review the causes and impact of drug shortages, and the final section will identify strategies, guidelines and recommendations that can be implemented to minimize the impact of drug shortages.

For the purpose of this report a drug shortage is defined as “any time when commonly stocked drugs are either not available to fill a prescription in a pharmacy, or when distributors or manufacturers are unable to supply a drug.”<sup>7</sup>

## Drug Shortages in Canada

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It is difficult to quantify and determine the extent of drug shortages in Canada because manufacturers are not required to report disruptions in drug supply to Health Canada and because there is no single accountable Canadian organization that provides system-wide drug distribution oversight.<sup>3</sup> Nonetheless, Canadian health practitioner associations<sup>3,6</sup> and the media<sup>4,8-10</sup> provide reports of drug shortages.

In December 2010, the Canadian Pharmacists Association (CPhA) published the results of a national survey on drug shortages.<sup>3</sup> The survey results are based on the opinion of more than 427 pharmacists (representing approximately 1.4 per cent of all Canadian pharmacists<sup>11</sup>). The report asserts that drug shortages are having a “detrimental impact on the health of Canadians and the ability of pharmacists to care for patients”. Manufacturers’ reluctance to share information is recognized as a significant barrier to increasing the awareness of drug shortages. The report points to the US Center for Drug Evaluation and Research’s Drug Shortage Program as a potential model from which Canada can learn. The 2010 report compared the drug shortages with a similar 2004 CPhA report<sup>7</sup> and noted that current drug shortages are “more widespread and prolonged.”

In March 2010, the Saskatchewan College of Pharmacists conducted a provincial survey<sup>6</sup> of 159 community pharmacy managers on the disruption in supply and/or shortages of prescription drugs. The survey identified 15 drugs that accounted for 75 per cent of the reported shortages. Ninety-one per cent of survey respondents reported that shortages were due to manufacturing problems and that no advance warning was issued by manufacturers on impending shortages.

The Canadian Anesthesiologists’ Society is currently investigating disruptions in the supply of propofol to determine whether its supply status meets the definition of a drug shortage.<sup>12</sup> The society is also concerned about the discontinuation of sodium thiopental.<sup>10</sup> Although there are therapeutic alternatives to sodium thiopental, it is the anesthetic commonly used for geriatric, cardiovascular, and obstetric patients.<sup>10</sup> Shortages of these two drugs could lead to the cancellation of surgeries and other medical procedures.

The Canadian Society of Hospital Pharmacists has expressed concern about drug shortages, particularly for drugs that do not have therapeutic alternatives.<sup>8</sup> The Canadian Medical Association has suggested that a national drug strategy is needed to oversee drug shortage issues and to prepare for shortages.<sup>4</sup>

## International Drug Shortages

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### United States

Globalization of the pharmaceutical industry has made supply disruptions for some drug products an international concern.<sup>3</sup> Drug shortages encountered in the US, may be a good indicator of shortages in Canada, as the drug inventories between the two countries are integrated.<sup>13</sup>

Recent drug shortages in the US have been described as “life threatening”<sup>14</sup> and are believed to be the worst in 20 years.<sup>15</sup> As of February 6, 2011, approximately 52 drugs have been reported on the Food and Drug Administration’s Current Drug Shortage list.<sup>16</sup> The reasons reported for the shortage were manufacturer delays in 30 cases and increased demand in 11 cases. As of February 9, 2011, the American Society of Health System Pharmacists (ASHP) lists more than 150 drugs as being in short supply.<sup>17</sup> The discrepancies between the FDA and ASHP lists are likely due to the fact that the FDA list is reliant on self-reported drug shortages from manufacturers, while the ASHP receives input from its members and others responsible for managing drug product inventories. These lists are ever changing as shortages are resolved and new drugs in shortage are added.

The Drug Shortage Program, within the Center for Drug Evaluation and Research, addresses “potential or actual shortages of prescription, over-the-counter, or generic drugs that have a significant impact on public health.”<sup>16</sup> The Drug Shortage Program works with drug manufacturers, review divisions, compliance and other departments of the FDA to manage product shortages.

The FDA has limited authority to resolve drug shortage issues because drug manufacturers are obliged to report only discontinuations of single-source, medically necessary drugs. New legislation is designed to change this. The *Preserving Access to Life-Saving Medications Act*, introduced into the Senate in February 2011, would require drug manufacturers to give early notification to the FDA on incidents that could cause a drug shortage. The legislation would direct the FDA to provide up-to-date public notification of drug shortages and actions taken to address them. The legislation

would also give the FDA the authority to require early notification from drug manufacturers when they decide to limit or discontinue drugs.<sup>18</sup>

From July 2010 to September 2010, the Institute for Safe Medication Practices (ISMP) polled more than 1,800 US health care practitioners to determine their experiences with disruptions in drug supplies. Respondents reported that the increase in volume of “critically important” drug shortages was a major concern. The survey revealed that two patient deaths had been attributed to dosing errors from the use of an unfamiliar alternative to morphine.<sup>14</sup> It was noted that substitute drugs are often difficult to find and the sudden demand for them can lead to a shortage in their supply.<sup>9</sup> In addition, the lack of advanced warning about an impending shortage and the number of health care practitioner hours lost to searching for therapeutic alternatives were major concerns.<sup>19</sup>

In November 2010, a Drug Shortage Summit was jointly held by the American Society of Anesthesiologists, the American Society of Clinical Oncology, the ASHP, and the ISMP. Initial recommendations for managing shortages were developed during the summit. Participants commented on the need for improved communication between stakeholders in the drug supply chain and health care providers.<sup>20</sup>

In the US, sterile injectable products have been particularly susceptible to shortages. According to data collected in 2008 by the FDA’s Drug Shortage Program, 35 per cent of all drug shortages involved sterile injectable products. In 2009, this increased to 46 per cent. This growth is believed to be partly a result of the consolidation of industry involved in making generic sterile injectable products, which is now limited to one or two companies.<sup>21</sup>

Until 2009, there were three manufacturers of propofol: Teva Pharmaceuticals, Hospira, and APP Pharmaceuticals. In early October 2009,

Hospira recalled their product because of “particulate matter in the vials.” This was followed in late October 2009 by a Teva recall of the same drug due to possible microbial contamination. This left one company to supply propofol to the entire US market.<sup>8,22</sup> As of May 2010, Hospira had not yet returned propofol to the market; however, an update in January 2011 reported intermittent backorders but continued improvements in supply. Teva announced in May 2010 that it would no longer manufacture the drug citing a difficult manufacturing process with little or no profit.<sup>22</sup>

The FDA dealt with this shortage by exercising its regulatory enforcement discretion by temporarily allowing the importation of an unapproved drug, Fresenius Propoven 1%, a propofol product approved in other countries. The FDA inspected the manufacturing facilities and evaluated the quality of the product to assure safety before allowing this temporary importation.<sup>22</sup>

The causes of sterile injectable product shortages in the US during the period of January 2010 to October 2010, are captured in Table 1.<sup>20</sup>

### Europe

Drug shortages in the United Kingdom (UK) have been linked to its weakened currency.<sup>23</sup> In particular, pharmacists have been selling drugs intended for patients in the UK to European markets where profits are more lucrative.<sup>23,24</sup> In an effort to prevent pharmacists from hoarding, repackaging and selling UK supplies to European countries, a practice known as “parallel trading,” manufacturers and wholesalers have imposed quotas on the volume of drugs that UK pharmacies can purchase. While this is difficult to monitor, individual pharmacies are being watched for unusually large orders, which might be an indicator of illegitimate trading. Several years ago, European countries were parallel trading with Britain, but with the weakening of the British currency, the situation has reversed.<sup>25</sup>

Table 1: Causes of Sterile Injectable Shortages in the US: January 2010 to October 2010 <sup>20</sup>	
Percentage Related to Reason of Shortage	Reason
42%	Product quality issues (includes particulate, microbial contamination, impurities, stability changes)
18%	Discontinuations
18%	Delays / capacity issues
9%	Raw material issues
5%	Closure of manufacturing facilities
4%	Component problems / shortages
4%	Increase in demand due to another drug shortage

In an effort to keep track of drug shortages, the UK’s Pharmaceutical Services Negotiating Committee (PSNC) keeps an inventory of drugs in shortage similar to the FDA’s Current Drug Shortage list.<sup>16</sup> Along with maintaining the drug shortage list, the PSNC has created contingency plans with manufacturers for dealing with sourcing drugs in shortage.<sup>24</sup>

The UK’s Department of Health has issued guidelines to address supply and distribution problems.<sup>26</sup> As well, in December 2010, the Department of Health produced a guideline to inform manufacturers, wholesalers, NHS Trusts, registered pharmacies, and dispensing doctors of their key legal and ethical obligations in relation to the supply and trading of drugs.<sup>27</sup>

Very little has been reported on drug shortages in Europe, with the exception of the UK. According to the European Medicines Agency (EMA), two drugs are in short supply: agalsidase beta and imiglucerase, both of which are manufactured by Genzyme in the US.<sup>28</sup> To help manage this shortage, the EMA’s Committee for Medicinal Products for Human Use issued temporary health care practitioners recommendations regarding patient prioritization for these drugs.<sup>29</sup>

According to the European Commission directive 2001/83/EC, Article 23a, market

authorization holders for products marketed in Europe Union member states are required to give two-months notification to regulatory authorities when market access to a product will be temporarily or permanently interrupted.<sup>30</sup>

**Australia**

While drug shortages have been noted in Australia, they do not appear to be extensive. According to the Therapeutic Goods Administration (TGA) Advisories Group, there is currently a shortage of heparin,<sup>31</sup> methadone,<sup>32</sup> and an anticipated shortage of indomethacin.

In response to the heparin shortage, Australia’s Office of Health Protection issued a guideline to clinicians to inform them of alternative anticoagulants.<sup>31</sup>

Methadone tablets have been recalled in Australia because of manufacturing quality control issues. Carbidopa-levodopa, manufactured by Merck Sharp & Dohme (Australia), went into shortage in December 2009. The manufacturer issued a notification that the issue would not be resolved until 2011, depending on regulatory approval.<sup>33</sup>

It is noteworthy that the TGA and the FDA have a cooperative arrangement regarding the exchange of information on current good manufacturing practices that may affect drug shortages in either country.<sup>34</sup>

**New Zealand**

The Pharmaceutical Management Agency of New Zealand (PHARMAC), a stand-alone crown entity accountable to the Minister of Health, works on behalf of New Zealand’s District Health Boards to manage the funding of community drugs.<sup>35</sup> Through its website, New Zealand’s drug regulatory body Medsafe, refers the public to PHARMAC regarding drug shortage issues.

PHARMAC is involved directly with the drug supply chain. Manufacturers are contractually obliged to notify PHARMAC if inventories fall below a two-month supply and if they become aware of potential shortages.<sup>36</sup> As well, manufacturers are liable for any additional costs accrued in sourcing alternative products, including the cost of replacement drugs.<sup>37</sup> In

the past, drug shortages have been blamed on the procurement process and PHARMAC's involvement:<sup>38</sup> however, no recent news stories could be found regarding this issue.

### Causes and Impact of Drug Shortages

The drug supply chain is the means through which prescription drugs are delivered to patients. It includes raw materials suppliers, drug manufacturers, wholesale distributors, group purchasing organizations, pharmacies, and drug regulators. Many factors can influence a drug shortage and often there are multiple causes that can affect the shortage of a single drug product. The drug supply system is complex and includes multiple organizations that play varied and occasionally overlapping roles in drug distribution and contracting.<sup>39</sup>

### Raw and Bulk Material Issues

The unavailability of raw or bulk materials used to make drugs contributes to drug shortages<sup>20</sup> and is believed to be particularly problematic when an active ingredient is obtained from a single raw material supplier.<sup>40,41</sup>

There are a number of causes of raw material supply disruptions. These may include:

- contamination of raw materials by disease or pollution<sup>41</sup>
- harm to raw materials caused by climatic or other environmental changes<sup>42</sup>
- complicated processing practices (e.g., extraction process from a natural source such as tree bark)<sup>43</sup>
- damage caused during the harvest, storage or transportation of raw materials.<sup>41</sup>

The sourcing of raw materials outside of the US is believed to be a major weakness in the drug supply chain.<sup>44</sup> Notably, one of the greatest threats to the supply chain anticipated during the next five years is thought to be contaminated raw materials and nonconformity to established standards.<sup>44</sup>

The inability of raw material processing facilities to consistently observe good manufacturing practice can result in regulatory authorities closing them down.<sup>20</sup> This is more commonplace in countries where regulatory and safety standards are not well observed.

Approximately 80 per cent of the active ingredients used in US and European drugs are currently manufactured in China and India,<sup>45</sup> countries that are believed to have less stringently enforced safety and regulatory standards than western regulatory bodies.<sup>46</sup>

As well, there is an increasing trend in China for drug raw material manufacturers to register themselves as chemical companies, a practice that gives them immunity to the scrutiny of Chinese drug regulatory authorities.<sup>47</sup> The heparin incident of 2008 is an example of how a Chinese raw material manufacturer was able to produce active ingredients for heparin even though it did not have the necessary certification to do so. A contaminated batch of heparin was sold to Baxter International, but the source of the contamination originated from the Chinese raw material supplier. The contaminated heparin was responsible for approximately 20 deaths and more than 350 adverse reactions in patients in the US.<sup>48</sup>

### Manufacturing Issues

There are numerous manufacturing issues that can create and/or contribute to drug shortages. Single-source drug products are the most vulnerable to shortages, although multi-source products are also susceptible. The latter is particularly the case if the primary manufacturer is affected, since less dominant market participants may not have the resources to supplement the shortfall.<sup>43</sup>

Drug shortages are often difficult to predict because manufacturers are reluctant to share details of shortages. This reluctance is largely due to a fear of losing competitive advantage<sup>6</sup> or due to public relation, legal and other considerations.<sup>49</sup> It is believed that this lack of transparency can actually intensify drug shortages because contingency plans and strategies cannot be effectively implemented to manage them.<sup>3,42,50</sup> Manufacturers may also be concerned that if they announce a shortage, wholesale distributors and pharmacists may hoard supplies of a drug, a practice that can intensify the impact of a drug shortage.

Identified causes of manufacturing disruptions affecting drug supply include:

- Unanticipated surges in demand for particular products<sup>16</sup> due to the approval

of a new indication, usage changes as a result of a new evidence-based practice or new clinical guidelines, or a sudden outbreak of disease.<sup>50</sup>

- Changes in production formulations.<sup>16</sup>
- Changes or problems in the production process, which may include regulatory good manufacturing process enforcement actions.<sup>42</sup>
- Limited manufacturing capacity – often multiple products are produced on the same equipment, which means that an increase in production of one product will usually result in a delay for production of another.<sup>43,51</sup>
- Temporary or permanent discontinuations of products as manufacturers shift production or reallocate resources.<sup>3</sup>
- Voluntary recalls initiated by manufacturers because of potential problems with a drug or manufacturers raising their own quality standards requiring time to comply with<sup>20</sup> (voluntary recalls are usually short-term situations).
- Complex manufacturing processes, such as those used to make sterile injectable products.<sup>51</sup>
- Antiquated manufacturing equipment<sup>42</sup>
- A business decision to cease production because of lack of financial return, poor demand, or potential safety concerns.<sup>52</sup>
- Industry increasingly manufacturing for a global market – where production decisions for products and market places have become increasingly complex.<sup>53</sup>

There are numerous business decisions that can impact drug shortages. The global economic downturn, patent expirations, and a dearth of pipeline innovations have driven manufacturers to seek internal efficiencies.<sup>54</sup> Many of these efficiencies have been found in the form of job cuts. In 2009, 23,000 jobs were lost to restructuring in the US pharmaceutical industry.<sup>55</sup>

Industry mergers are another means of creating internal efficiencies. In 2009, more than 27,700 jobs were lost in the US pharmaceutical industry as a result of mergers.<sup>55</sup> When companies merge, less profitable product lines

are often reduced or discontinued<sup>51</sup> and sometimes manufacturing facilities close.<sup>42</sup> Mergers of companies with similar product lines will see product consolidation, possibly resulting in changing a multi-source product into a single-source product. These consolidation practices result in fewer companies manufacturing drugs, leaving markets vulnerable to shortfalls.

The pharmaceutical industry is currently facing the loss of a large number of patent protections. Drugs worth US\$15.3 billion will face generic competition this year,<sup>54</sup> and in 2012, US\$33.2 billion will be lost due to patent expirations.<sup>54</sup> This loss in revenue may result in more industry mergers, restructurings, and discontinuations of drugs.

It is believed that there was a time when global drug manufacturers protected certain service products in the interest of patient care: “small and commercially less interesting niche products that were made available as part of a wide product range.”<sup>56</sup> It appears that this philosophy has changed and, products such as sodium pentothal, a single source anesthetic that has a small profit margin, are now discontinued.

### Wholesale and Distribution Issues

Wholesale and distribution issues can play a role in drug shortages. Many of these issues relate to inventory management practices. For example, some manufacturers and wholesale distributors may minimize end-of-quarter or end-of-year product inventories as an inventory management strategy. Manufacturers and wholesalers may also limit the shipments of products based on yearly quotas, a practice that can result in product shortages at the pharmacy level.<sup>42</sup>

In addition, many manufacturers, wholesalers, and pharmacies use “just-in-time” inventory control practices that involve keeping minimal supplies of drugs in stock. While this is an attractive cost-saving strategy,<sup>7</sup> it is a practice that can contribute to drug shortages due to an overall reduction of readily available drug inventories.<sup>20</sup>

In order to maintain profit margins, wholesalers may stockpile lower-priced inventory in anticipation of upcoming manufacturer price

increases. Similarly, rumoured price increases could lead to stockpiling at the pharmacy level.<sup>42</sup> Stockpiling can also occur because wholesalers and pharmacies believe that a supply shortage is forthcoming, such practices can actually prolong a disruption because they create an artificial shortage.<sup>7</sup>

Delays in the distribution chain from drug manufacturers to wholesalers, and from wholesalers to health system pharmacies could also contribute to drug shortages. These delays could be due to factors such as lengthy contract negotiations or delivery delays.<sup>42</sup>

Price differences between jurisdictional drug formularies, where the price for the same product differs from jurisdiction to jurisdiction, may result in wholesalers selling drugs preferentially to provinces where profits are more lucrative. This practice may account for the regional differences in drug availability. Contractual agreements with wholesalers and group purchasing organizations may also account for regional variations in drug availability.<sup>20</sup>

It is noteworthy that in Canada and the US, when drug manufacturers sell products to self-distributing pharmacy chains and wholesalers, they relinquish title rights to the product. Manufacturers have no power to redistribute products between buyers once the title transfer has taken place. Thus, shortages that may occur after products have been sold by the manufacturers are not only beyond their control, but are also beyond their knowledge.

### Provincial Reimbursement Policies

Generic drugs account for more than 50 per cent of all Canadian prescription drugs, and with more brand name drugs coming off patent, this number is expected to rise.<sup>57</sup> Shortages of generic drugs are increasing in frequency in Canada<sup>58</sup> and there is concern that recent reforms to control generic drug costs may have contributed to the problem. In 2010, provincial drug plans in Ontario, Quebec, and other provinces capped the price of generic drugs at 25 per cent of brand name equivalents pricing, down from 50 per cent.<sup>59</sup>

The substantial cut in profit margins associated with price capping reforms may discourage global drug manufacturers from continuing the

production of drugs with profit margins that are already under performing. The Canadian Generic Pharmaceutical Association denies that current generic drug shortages are a response to provincial price capping reforms,<sup>60</sup> stating that shortages predate the legislation that was passed in July 2010. A statement released by the group cited raw material shortages, changes to regulatory standards and requirements, production issues, and changes in production equipment and processes as the contributing factors to generic and brand name drug shortages.<sup>60</sup>

### Regulatory Issues

Strict enforcement of good manufacturing practices and other related regulations by drug regulatory bodies may play a role in drug shortages.<sup>61</sup> Various Apotex drug shortages occurred after Health Canada and FDA regulatory inspections that resulted in the voluntary recall of several products.<sup>61</sup>

In response to the heparin contamination issue in 2008, the FDA increased the number of manufacturer inspections it performs in China and India.<sup>62</sup> In 2009, the FDA had two medical product investigators in China, a country that has more than 900 drug manufacturing facilities,<sup>63</sup> to ensure compliance with current good manufacturing practices. The FDA also has two inspectors in India, where there are approximately 502 drug manufacturing sites.<sup>63</sup> As the FDA increases its resources to manage these inspections, it is possible that the closure of plants that are not in compliance with regulatory standards may contribute to drug shortages.

A joint initiative between the FDA, TGA, and EMA in 2008, set-up partly in response to the heparin contamination issue, may also have an impact on drug shortages. The purpose of the collaboration is to create a joint inspection program for international active pharmaceutical ingredient manufacturers to improve transparency and efficiency in inspection practices and reduce duplication of inspections.<sup>64</sup>

The 2010 Drug Shortages Summit in the US concluded that FDA regulatory barriers and ambiguities, including the lack of regulatory power to require manufacturer drug shortage notification and other actions, were considered

to be significant contributors to drug shortages.<sup>20</sup> Health Canada does not require manufacturers to notify them of expected product withdrawals. Similarly, no statutory authority is in place in Canada that can enforce manufacturers to report notifications on the disruptions in the supply of medically necessary drugs. The new legislation, recently introduced into the US Senate, the *Preserving Access to Life-Saving Medications Act*, will help address this issue for the FDA.<sup>18</sup>

New regulatory requirements from Health Canada are also believed to have contributed to drug shortages; in particular, the new policy for Notifiable Changes. Under the old Notifiable Changes policy, if a manufacturer did not receive a written objection from Health Canada within 90 days, the manufacturer was able to proceed with the change. In September 2009, Health Canada implemented a policy change that would help them to more effectively manage risks associated with changes to drugs. The new reform eliminated the 90-day default clause and now requires drug manufacturers to wait for Health Canada's review and approval before implementing changes.

It is not uncommon for manufacturers to make such changes to drugs. In 2009, 1,073 submissions were received by Health Canada by drug manufacturers for notifiable changes.<sup>65</sup> These are submissions manufacturers must make to Health Canada for changes to previously approved drugs. Many of these changes are made to "improve the quality of the drug product or the efficiency of the manufacturing process, or they could be made for marketing considerations. Changes to the labeling of a drug product could include adding new indications, improving the management of risk for a product by adding warnings, limiting the target population or changes to dosage regime etc..."<sup>66</sup>

Although Health Canada's intention is still to review changes within a 90-day period, this timeline is not routinely maintained. For example, in the third quarter of 2010, drug manufacturers submitted 94 chemistry and manufacturing notifiable changes to Health Canada. Of the 94 submissions, nine met the targeted 90-day deadline.<sup>67</sup> It is not known what the average turn-around time is for

notifiable changes, but the potential for them to contribute to drug shortages is apparent.

The backlog of new drug applications awaiting regulatory approval, that could be potential alternatives to drugs in short supply, can also contribute to drug shortages.<sup>20</sup>

### Impact of Drug Shortages

The main clinical impacts of drug shortages are felt by patients, pharmacists, and physicians.

### Patients

The main concern with drug shortages is that patient care may be compromised.

For drugs with no therapeutic alternative, the lack of drug therapy may lead to poor patient outcomes. Even for drugs that have therapeutic options, patients may experience different or more severe side effects.<sup>2</sup> In some instances, this has led to patients refusing or being unable to take alternative medications.<sup>3</sup>

Patient health outcomes were a concern for 70 per cent of the pharmacist respondents in the 2010 CPhA Drug Shortage survey. From patients' perspectives, the most commonly reported concerns were anxiety, confusion, frustration, and anger, as a result of changes to drug prescriptions and the need for more frequent pharmacist and physician visits.

Drug shortages can potentially create procedure delays, cancellations, and prolonged patient hospital stays.<sup>68</sup> Patients may be forced to pay out-of-pocket if prescribed alternative drugs are not covered by their drug plans<sup>3</sup> or pay higher prices for the alternative.

In addition, changing therapy or the use of a less familiar alternative drug therapy may raise patient safety issues. Findings from the 2010 Institute for Safe Medication Practices survey support this concern. Approximately 35 per cent of the polled pharmacists believed that patients in their facilities had encountered a "near miss" medication error during the past year due to a drug shortage. Roughly 25 per cent reported actual errors, and 20 per cent reported adverse patient outcomes.<sup>19</sup> For example, because of the morphine shortage in the US, two patients died as a result of being prescribed and administered intravenous

hydromorphone at the intended dose for morphine.<sup>19</sup> Furthermore, the prevalence of errors and adverse patient outcomes caused by drug shortages is felt to be under reported.<sup>19</sup>

### Pharmacy Services

The main impact of drug shortages on pharmacy services is the amount of time spent by staff repeatedly checking for drugs that are in shortage. Pharmacists are believed to be spending between 30 minutes and three hours per shift sourcing drugs.<sup>3</sup> Some hospital pharmacies have employed dedicated staff specifically to monitor and help resolve supply issues and to research alternative sources and alternative therapies.

Drug shortages divert pharmacists away from spending time on direct patient care. There is concern that this lack of patient care could potentially lead to lapses in drug use and potential increases in drug-related problems, especially when an alternative drug is substituted for a drug in shortage.<sup>2</sup> Alternative drugs may require different dosing, preparation, and storage.

There may also be a financial burden associated with alternative drug therapies as they are often more costly to the pharmacy department.<sup>69</sup>

### Physician Impact

Drug shortages can compromise the quality of patient care. Physicians may be forced to use alternative therapies that are often not supported by evidence-based guidance and may require different prescribing parameters and patient monitoring practices. These new practices require physicians to quickly learn the characteristics and side effects of second, third, and even fourth-line drug therapies and may lead to prescribing errors.

Physicians may also be forced to prioritize patients in order of those with the most urgent need of drugs that are in shortage. When there is only a limited supply of a drug and therapeutic alternatives for specific patient groups are not optimal, physicians will prioritize the drug in limited supply for specific patient groups.<sup>20</sup> For example, during the acyclovir shortage, some hospitals limited the use of acyclovir to confirmed cases of neonatal

herpes simplex virus (HSV) meningitis, and used ganciclovir for cases when HSV meningitis was suspected, but not confirmed.<sup>69</sup>

Risk management and liability are also important considerations for physicians who could potentially be accused of providing suboptimal patient care as a result of a drug shortage.

### Strategies to Manage Drug Shortages

Proactive strategies are required to help prevent, minimize, and/or manage the impact of drug shortages.

Canadian guidelines for the management of current and future drug shortages have been developed by the CPhA.<sup>1,3</sup> These guidelines include the following recommendations to address drug shortages:

- Prioritize patient needs in the business plans and strategies of all stakeholders in the drug supply chain.
- Expand scopes of responsibility for pharmacists to include adapting new and refill prescriptions and, in collaboration with doctors, to be allowed to substitute equivalent drugs.
- Empower pharmacists to make sure patients are properly managed after drug shortages have been resolved to reduce any risks or safety concerns resulting from substitution of therapy.
- Improve collaboration and communication between drug manufactures and other stakeholders.
- Have government involvement, at the federal and jurisdictional level, to promote an adequate supply of drugs and incentives for manufacturers and wholesalers not to discontinue product lines.
- Create new contractual agreements between provinces, hospitals, and other agencies to ensure that their contracts with manufactures and suppliers include supply guarantee clauses.
- Discourage arbitrage (“the practice of purchasing drugs in one jurisdiction and selling to another”).

The CPhA has also developed Assessment and Patient Management Guidelines that include checklists and strategies to help pharmacists manage drug shortages.<sup>3</sup>

US guidelines on drug shortage management have been published by ASHP,<sup>42</sup> instructing pharmacists to validate drug shortages, search for alternatives, investigate implications of compounding products, and educate patients on drug alternatives and costs.<sup>42</sup> Those in charge of health systems are encouraged to conduct a threat analysis and develop contingency plans in advance of a drug shortage.<sup>42</sup> ISMP advocates for the use of risk management strategies, including failure mode and effects analysis, and a discussion of ethical considerations.<sup>70</sup>

Other sources suggest that the FDA expand its authority to require manufactures to (confidentially) notify the FDA when a product has a single-source active pharmaceutical ingredient or supplier, and notify them of planned market withdrawals.<sup>20</sup> To help manage drug shortages, the FDA has an allocation program in place to limit the distribution of remaining inventory until resolution of the drug shortage.<sup>43</sup>

Guidance to prevent drug shortages in the UK is focused mainly on policies to discourage parallel trading. The UK Department of Health has published guidance papers regarding drug shortages. The enforcement of wholesaler licensing agreements is being more strictly monitored with breaches facing regulatory and/or criminal prosecution.<sup>27</sup> These regulations require the appropriate and continued supply of relevant medicinal products so that the needs of patients in the UK are covered.<sup>27</sup> Manufactures supplying UK wholesalers must verify that the drugs requested are needed by UK patients. Pharmacists and licensed wholesale dealers are encouraged to keep fully documented files of their transactions so that medicinal products in wholesale supply are kept in the licensed distribution chain.<sup>27</sup>

Drug manufacturers represented by the Association of the British Pharmaceutical Industry (ABPI) and the British Generic Manufacturers Association (BGMA) are required to designate one person to deal with supply issues in each company and create written procedures to avoid, identify, and deal with

product shortages.<sup>71</sup> Manufacturers are called to take action and curb “inflexibility, enforced by quotas” when managing the UK supply, which is said to have contributed to a situation where demand has surpassed existing supply.<sup>72</sup>

In February 2011, the UK Department of Health issued best practice guidance to ensure the efficient supply and distribution of drugs. The guidance recognizes the importance of regular communication between manufacturers and wholesalers in an effort to increase awareness of supply and demand issues. The creation of contingency plans for the sourcing of supplies for all members of the drug supply chain, regarding supply difficulties were noted as being of importance. As well, drug prescribers are advised to consider alternative drugs for patients, and encourage patients to request prescriptions for drugs that have been identified as being in shortage as early as possible.<sup>26</sup>

## Conclusion

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The true causes of Canadian drug shortages are unknown. However, drug shortages are a reality and the causes are believed to be multifactorial. Currently, the Canadian generic drug market appears to be experiencing more shortages than the brand name market. Although drug shortages appear to predate provincial generic price-capping legislation, it is difficult to know to what extent because drug shortages in Canada are currently not routinely or centrally monitored.

Industry mergers and consolidations resulting in single-source products, business decisions to discontinue manufacturing of minimally profitable products and just-in-time inventory management practices across the supply chain can amplify the effects of drug shortages.

From a policy perspective, an awareness of the different dynamics between the supply chain players and the financial motivations that drive business decisions is critical to an appreciation of the causes of drug shortages and the steps that can be taken to minimize and avoid them.

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