

Recommendations of the Working Committee on Drug Shortages

DRUG SHORTAGES

A PUBLIC HEALTH ISSUE THAT DEMANDS
A COORDINATED RESPONSE

This paper was approved in March 2012 by the boards of directors of the Ordre des pharmaciens du Québec, Collège des médecins du Québec, Association des pharmaciens des établissements de santé du Québec, and the Association québécoise des pharmaciens propriétaires.

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INTRODUCTION

In 2011, greatly concerned by the impact of drug shortages on the protection of the public, the board of directors of the Ordre des pharmaciens du Québec formed a Working Committee to examine the reasons for drug supply disruptions and propose mechanisms and solutions that could be part of a national strategy. The Committee began its work in March 2011.

Although the professional orders have the regulatory power to oversee the practice of their members, they do not have the necessary legislative authority to intervene with the pharmaceutical supply-chain stakeholders. The same is true of the professional associations. Determined to fulfill their collective responsibility to patients, the Committee members nevertheless decided to tackle this crucial issue to propose solutions, and, above all, influence the stakeholders who possess the power to make the required changes.

The Committee based its work on the premise that drugs, like water, are exceptional consumer products that merit specially tailored controls. To this end, regulatory agencies and decision-makers must always consider the impact of their decisions, or lack of decisions, regarding access to drug products. People often forget that drugs can save lives, relieve suffering and prevent disease. Lack of drug availability has serious repercussions for patients; we are all concerned by the growing prevalence of these shortages in our health system.

Activities of the Committee

The Working Committee on Drug Shortages adopted a rigorous approach. To come up with solutions for optimal impact, Committee members wanted to improve their understanding of the causes and consequences of the shortages. After completing a literature review and considering solutions adopted by other countries, they drafted a preliminary report. This report was presented to the boards of directors of the participating organizations in fall 2011.

The Committee then held a series of meetings, between December 2011 and January 2012, with the principal drug supply-chain stakeholders, legislative agencies and other key stakeholders to present and obtain feedback on its initial recommendations. Groups that agreed to take part in the consultation:

- ✓ Industry: Canadian Generic Pharmaceutical Association and Canada's Research-Based Pharmaceutical Companies
- ✓ Government bodies: Health Canada, ministère de la Santé et des Services sociaux du Québec
- ✓ Distributors: McKesson Canada, McMahon, Groupe PJC, LSU Boucherville, Kohl & Frisch, Shoppers Drug Mart
- ✓ Public agencies: Régie de l'assurance maladie du Québec, SigmaSanté, Approvisionnement – Montérégie, Coopérative des services regroupés en approvisionnement de la Mauricie et du Centre-du-Québec, Corporation d'approvisionnement Laurentides-Lanaudière, Approvisionnement des deux Rives

In general, the consulted groups shared the Working Committee's objectives and were interested in collaborating. They were all in agreement with the description of the problem. Most discussions centred around the recommendations and the proposals for implementing them.

In this final report, the Working Committee has taken into account many of the comments and suggestions made during these consultations.

SUMMARY

Drug shortages are not new. What is unprecedented is the number, duration and impact of shortages in recent years. This is why our organizations decided to join together to develop measures to guarantee that Quebecers have better access to the medicines they need.

The aim of this report is to further the understanding of drug shortages and recommend solutions to reduce their scope and impact.

SUMMARY OF THE PROBLEM

Drug shortages vary in nature. They can be qualified as “partial” when they involve one distributor or manufacturer, or “total” when the drug is no longer available on the market.

They can be very simple to manage (order from another distributor) or very difficult to resolve (obtain approvals to order a drug marketed in Europe, calibrate automatic distribution systems for the new product, notify practitioners in health institutions about a temporary substitute drug, format or concentration change, or any other potentially error-generating change, resume use of usual drug several days later, etc.). In health institutions, shortages of drugs administered by parenterally generate specific problems associated with the need for rapid intervention, and the essential role of these drugs in hospital interventions (surgeries), which necessitates the location of alternative therapies.

Last, they may be serious and jeopardize patients’ health because the substitute exposes them to more adverse side effects, because they may not understand the new dosage regimen or new therapies, or because there are no substitute therapies that meet their needs. The main causes of shortages are production stoppages or delays related to manufacturing, regulatory or economic constraints. This leads to an imbalance between supply and demand.

We now know that the impacts of shortages go beyond administrative management issues. In 2010, the Institute for Safe Medication Practices (ISMP) surveyed 1,800 US health professionals, revealing that in just one year, drug shortages caused over 1,000 incidents involving negative side effects or medical errors. In the fall of 2011, the Associated Press assessed the consequences of drug shortages and reported at least 15 deaths in 15 months in the United States. Closer to home, the recent injectable drug shortage forced at least 65 surgeries to be postponed. And these are just the incidents counted and reported by the media.

Given the frequency of shortages and the clinical risks caused by drug supply disruptions, it is now crucial that we consider this problem from another angle. It must now be perceived as a major public health issue.

SUMMARY OF RECOMMENDATIONS

It is the position of the Working Committee that a concerted effort by all concerned stakeholders is needed, and that the seriousness of the situation justifies the immediate implementation of solutions to mitigate the effects of shortages until more permanent solutions can be put in place.

<p>FEDERAL NATIONAL POLICY ON ACCESS TO MEDICALLY NECESSARY DRUGS</p>	<p>RECOMMENDATION 1 That federal, provincial and territorial health ministers develop a national vision and action plan to ensure access to medically necessary drugs.</p>
<p>RECOMMENDATION 2 That Health Canada adapt its regulations and programs to address the problem of drug shortages.</p>	<p>RECOMMENDATION 4 That legislation be passed requiring manufacturers to provide one year's advance notice before the voluntary discontinuation of a drug.</p>
<p>PROVINCIAL SHORTAGE COORDINATING ENTITY</p>	<p>RECOMMENDATION 5 That provincial health minister designate an entity to coordinate the management of drug shortages and necessary information on shortages.</p>
<p>RECOMMENDATION 6 That federal and provincial government policy include incentives to produce medicines in shortage and less profitable drugs.</p>	<p>RECOMMENDATION 7 That purchase contracts and refund agreements include incentives for guaranteed supply and penalize supply disruptions.</p>
<p>MANUFACTURERS</p>	<p>RECOMMENDATION 3 That manufacturers adopt responsible inventory management practices and ethical practices in situations of shortages.</p>
<p>DISTRIBUTORS</p>	<p>RECOMMENDATION 8 That distributors adopt distribution and inventory management practices that guarantee the safety of the supply-chain and ensure resiliency in responding to urgent or priority needs.</p>
<p>PHARMACISTS</p>	<p>RECOMMENDATION 9 That pharmacists responsibly manage their drug supply and facilitate the equitable usage of available medicines.</p>

ACRONYMS AND ABBREVIATIONS

ASHP	American Society of Health-System Pharmacists
PTA	Pharmacy Technical Assistant
FDA	Food and Drug Administration
DSC	Drug supply-chain stakeholders
ISMP	Institute for Safe Medication Practices
WHO	World Health Organization
RAMQ	Régie de l'assurance maladie du Québec
URPP	Unité de recherche en pratiques pharmaceutiques (practice-based pharmaceutical research unit, affiliated with the pharmacy department at Sainte-Justine Hospital and the hospital's research centre)

DEFINITIONS

Drug shortage

The FDA defines a drug shortage as “a situation in which the total supply of all clinically interchangeable versions of an FDA-regulated drug is inadequate to meet the current or projected demand at the patient level.”

Medically necessary

The FDA defines a medically necessary drug as “a product that is used to treat or prevent a serious disease or medical condition for which there is no other alternative drug, available in adequate supply, that is judged by medical staff to be an adequate substitute.”

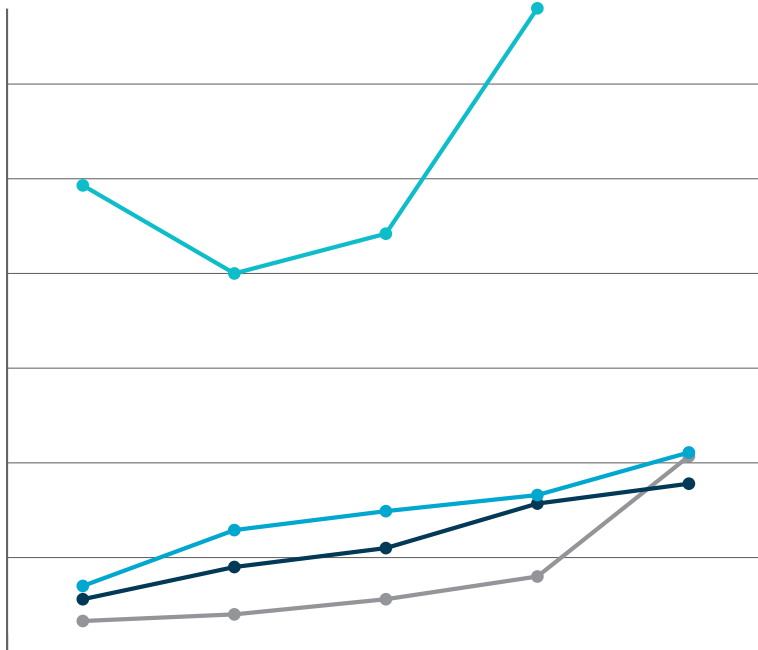
PRESENTATION OF THE PROBLEM

UNPRECEDENTED SHORTAGES

Since 2006, health professions have observed an unprecedented increase in the number of drug shortages, as the number quadrupled between 2006 and 2010. More than ever before, health professionals are grappling with highly problematic situations. Moreover, not only is the supply of a particular drug disrupted, but increasingly, the substitute product that would normally be used in its place is also in short supply or on the verge of becoming so.

Figure 1 provides a clear picture of the situation.

FIGURE 1
NEW SHORTAGE NOTIFICATIONS BY YEAR,
ACCORDING TO THE FDA, ASHP, URPP AND RAMQ



	2006	2007	2008	2009	2010
■ FDA	56	90	110	157	178
■ ASHP	70	129	149	166	211
■ URPP	493	400	442	680	
■ RAMQ	33	40	56	80	207

**“ THE INCREASE
IN THE NUMBER AND
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SHORTAGES IS OF
PARTICULAR CONCERN TO
HEALTH PROFESSIONALS
AND PATIENTS. ”**

In 2011, the FDA counted 250 drug shortages, a 40% increase over the previous year. Data are not yet available from the other agencies.

Drug shortage announcements vary from one agency to another because the FDA bases its report on manufacturers' voluntary notifications concerning "medically necessary" drugs, while the ASHP uses its members' reports on the full range of drugs.

In Quebec, the provincial health insurance board, RAMQ, has also noted the severity of the increase. From 33 shortages in 2006, the number of declared shortages rose to 80 in 2009 and 207 in 2011.¹ RAMQ only counts products covered by the public drug insurance plan, the Régime général d'assurance médicament; these figures therefore do not include many drugs that are often required in critical situations, but are only available in health institutions. Moreover, when no substitutes exist for the drug in short supply, the drug is not included in the compilation.

The Quebec-based site *Vendredi PM*² listed 110 drug shortages on February 3, 2012 (not counting different formats and dosages). Quebec data issued by the group purchasing organization SigmaSanté, Canada's third largest drug purchasing group, also reports an increase in the incidence and duration of shortages.³

This website was consulted before the shortages caused by the fall in production of sterile injectable drugs at the Sandoz plant in Boucherville.

SHORTAGES LASTING FOR LONG PERIODS

The increase in the number and duration of drug shortages is of particular concern to health professionals and patients.

The FDA estimates that the average period before a "medically necessary" drug shortage can be resolved is 105 days—over three months. The overall median period is around 62.5 days; the period for innovator products is 57 days and that for generic drugs is 71.5 days.⁴

According to the URPP, the average supply disruption of drugs used in the health institutions under study was roughly 108 to 130 days.⁵ These data also show that many shortages last for more than a year. In some cases, return dates are announced but not respected, leaving pharmacies, physicians and patients in the dark about when the products will actually return to the market.

AFFECTED MEDICATIONS: MEDICALLY NECESSARY AND RESTRICTED SUPPLY

Increasingly, the drugs vulnerable to shortages are medically necessary, meaning they are used to treat or prevent critical health conditions for which there exist no other therapies.

According to an FDA survey, out of 127 unavoidable shortages reported between January 2010 and August 2011, 93% involved medically necessary drugs and 41% were both medically necessary and sole source.

¹ Data from RAMQ.

² www.vendredipm.ca/ruptures-en-ligne-par-mckesson/ruptures-dapprovisionnement (Retrieved 3 February 2012).

³ Chiveri, A., Lebel, D., Bussi eres, J.F. *Perspectives des ruptures d'approvisionnement de m edicaments 2006-2010*. Professional Practice Conference, Canadian Society of Hospital Pharmacists, Toronto, February 2011. Available online at: www.vendredipm.ca/ressources

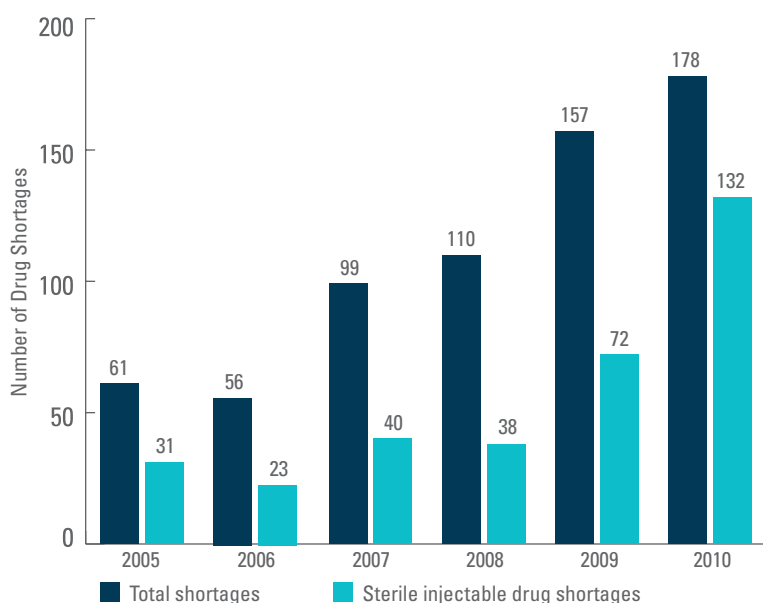
⁴ *A Review of FDA's Approach to Medical Product Shortages*, October 2011.

⁵ Chiveri, Note 3.

Injectable drugs: shortages with severely critical repercussions

FDA data from 2008 indicates that sterile injectable drugs represented 35% of all reported shortages. In 2009, this proportion rose to 46%.⁶ In 2010, it reached 74%.⁷ Articles published in the United States report that shortages of antineoplastic drugs, some broad spectrum antibiotics and anesthetics are of particular concern.⁸ The table below illustrates the scope of injectable drug shortages in the United States.

FIGURE 2
NUMBER OF US DRUG SHORTAGES FDA'S DRUG SHORTAGE PROGRAM HELPED ADDRESS, 2005-2010



FDA DATA FROM 2008 INDICATES THAT STERILE INJECTABLE DRUGS REPRESENTED 35% OF ALL REPORTED SHORTAGES. IN 2009, THIS PROPORTION ROSE TO 46%. IN 2010, IT REACHED 74%.

In February 2012, Quebec and several other Canadian provinces experienced a major shortage of sterile injectable drugs. The Sandoz plant in Boucherville, which supplies many hospitals and pharmacies, was forced to cut back production while it made changes to its facilities after receiving an FDA notice.

Since the manufacture of sterile injectable drugs is more complex, and thus more expensive, there are fewer companies making these products.

More generic than innovator drugs in shortage

A report from the IMS Institute for Healthcare Informatics⁹ on 168 drug shortages in 2011 showed that 83% of the drugs were generic. Indeed, drugs marketed before 2000, many of them medications produced solely by the generics industry, were especially affected by the shortages. This report also states that 50% of the drugs in shortage were produced by just one or two manufacturers.

An FDA report published in October 2011 mentioned that 50% of the shortages involved generic medicines and 43% were innovator drugs. Some 7% of the shortages involved products that were both generic and innovative.

⁶ Canadian Agency for Drugs and Technologies in Health. *Drug Supply Disruptions*, March 2011: No. 17.

⁷ See Note 4.

⁸ Chustecka, Z. «Ongoing Drug Shortages Hitting Oncology Hardest,» *Medscape Medical News*, December 2010.

⁹ *Drug Shortages: A closer look at products, suppliers and volume volatility*. Report by the IMS Institute for Healthcare Informatics, November 2011.

Cancer patients: victims of this situation

The IMS Institute for Healthcare Informatics reports that oncology drugs account for 16% of the drug shortages, while antibiotics account for 15%. These are the two categories most affected by the shortages.

In the FDA's report on 127 shortages reported between January 2010 and August 2011, 28% involved oncology drugs and 13% involved antibiotics.

COMPLEX AND MULTIPLE CAUSES

Most publications give the same causes for shortages.^{10,11} Appendix 1, on page 44, locates these factors within the supply-chain process. It also provides information on the supply-chain process, its entities and their respective roles.

An FDA report published in October 2011¹² presents the causes of 127 unpreventable drug shortages between January, 2010 and August 26, 2011.

TABLE 1:
CAUSES IDENTIFIED BY THE FDA FOR 127 DRUG SHORTAGES
BETWEEN JANUARY 2010 AND AUGUST 2011

Manufacturing quality issue	43%
Manufacturing or shipping delays	15%
Active ingredient or component shortage	14%
Business decision to discontinue production	8%
Loss of manufacturing site	5%
Demand increase	4%
Improper labelling	2%
Unknown cause	9%

¹⁰ ASHP Expert Panel, Fox, E.R., Birt, A., James, K.B., et al. «ASHP Guidelines on Managing Drug Product Shortages in Hospitals and Health Systems,» *Am J Health-Syst Pharm* 2009; 66(15):1399-406.

¹¹ American Society of Health-System Pharmacists, American Society of Anesthesiologists, American Society of Clinical Oncology, Institute for Safe Medication Practices. «Drug Shortages Summit Summary Report» [Internet]. Bethesda, Maryland: *American Society of Health-System Pharmacists*, 5 November 2010 [Retrieved 22 February 2011].

¹² See Note 4.

The causes of shortages in innovator and generic drugs are similar, although production and shipping delays seem to be more of an issue for generics (23% compared to 6%).

Quality issues seem to be more prevalent with injectable drugs (45% compared to 32%) and active ingredient shortages figure more prominently with non-injectable drugs (20% compared to 8%).

Principal causes noted in the literature

The following are the most commonly cited causes in the literature.

1. DECREASED SUPPLY

Decreased supply can be explained in a number of ways.

- ✓ Industry mergers and consolidations (manufacturers and distributors)
Globalization means that fewer manufacturers are producing drugs to cover a much larger territory: the entire planet. Three major generic injectable drug manufacturers supply 71% of the US market. Sole-source supply is often mentioned as a risk factor for drug shortages. The formation of large companies prevents smaller firms from co-existing and ensuring a balance in the market.
- ✓ Consolidations of purchasing groups, concentrating the purchasing activities of several regions in a small group.
- ✓ Production stoppages for non-compliance with manufacturing processes and recalls
 - Non-compliance with manufacturers' standards and recalls
 - Non-compliance with regulatory standards
- ✓ Production stoppages or delays due to changes in manufacturing procedures or transfers of production lines
- ✓ Production stoppages or delays due to business or economic considerations
 - Some products are no longer profitable due to price controls
 - Downsizing of product portfolios
 - Production of new more lucrative drugs, which limits the production capacity of less profitable products This situation is combined with heavy use of production capacity and dedicated production lines (oncology, antibiotics). The most recent oncology drug shortages in the US were linked to three production lines of two manufacturers.¹³

¹³
See Note 4.

“ CURRENTLY, THE SAME RAW MATERIAL PROVIDERS SUPPLY SEVERAL MANUFACTURERS AND FOR MOST DRUGS APPROVED BY HEALTH CANADA, THE LICENCE STIPULATES A SINGLE SOURCE FOR RAW MATERIALS. ”

2. INSUFFICIENT QUANTITIES OF RAW MATERIALS AND QUALITY ISSUES

Currently, the same raw material providers supply several manufacturers, and for most drugs approved by Health Canada, the licence stipulates a single source for raw materials. This means that in a shortage, the manufacturer cannot source raw materials elsewhere.

Moreover, supply is jeopardized by the fact that some raw material manufacturers do not meet good manufacturing practice requirements. China and India supply 80% of the raw materials used by manufacturers in the United States and Europe. In 2008, a large batch of heparin marketed by Baxter was contaminated. The explanation: a Chinese raw material manufacturer had registered itself as a chemical company, releasing it from regulatory oversight.¹⁴

3. INCREASED DEMAND, VOLATILITY OF DEMAND AND PRODUCTION

Other factors in drug shortages: new needs and emerging markets that generate an unanticipated demand and allocated quantities that are insufficient to meet actual needs. The risk of a shortage is accentuated when supply-chain entities, in particular, distributors and pharmacists, have little leeway with which to adapt to change, for instance, when they adopt the “just-in-time” management strategy to keep inventory down or when manufacturers base their production on conservative sales forecasts.

Regulatory requirements that complicate the production process

✓ Establishment of new drug formulations

An example of this is the new standards for evaluating the effectiveness of heparin, a powerful anticoagulant. These standards emerged following a manufacturer’s market approval submission featuring an evaluation using the most recent technological tools. Other manufacturers must now use the new technology to evaluate effectiveness, which can cause production delays that then lead to a shortage.

✓ Many drugs have been recalled from the market in the wake of new requirements for pharmaceutical companies to validate manufacturing procedures for drugs marketed prior to 1938; drugs are also recalled because of the impossibility of validating the conformity of old equipment.

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Canadian Agency for Drugs and Technologies in Health. *Drug Supply Disruptions*, March 2011: No. 17.

Absence of legislation on drug shortages

- ✓ Absence of legislation and drug shortage-related constraints imposed on manufacturers and distributors.

Currently no regulation exists that obliges the industry to give advance notification of drug product discontinuation or an anticipated interruption of the supply. This means that it is impossible to implement measures—national, provincial, and local—to prevent shortages and manage risk before the drug becomes unavailable. This is particularly problematic with regard to medically necessary and sole-source drugs.

- ✓ Delays in regulatory decisions and unpredictable turnaround time for processing approval requests

Manufacturers that make submissions for Notifiable Changes in a drug's manufacturing process or their raw material supplier must wait for approval before beginning production. Health Canada's deadline is 90 days. In the third quarter of 2010, only nine applications out of 94 met the 90-day deadline.¹⁵

- ✓ Foreign regulatory bodies can also affect the local supply. The Sandoz case showed that the decision of a foreign regulatory body—in this case, the FDA—can have a major impact on the local supply of drug products. In this particular case, the FDA was concerned about a product that is not even sold in Canada: testosterone 200 mg/ml. Production at the Sandoz plant was nevertheless affected, as we know only too well.

Distribution and access practices

- ✓ Inventory minimization practices

New management trends (just-in-time, minimizing strategies, etc.) create added efficiency for firms but increase the risk of insufficient reserves to meet drug shipping needs in the event of shortages or unanticipated events. These practices are in effect across the supply-chain, in community pharmacies, health system pharmacies, manufacturing firms and distributors.

Other practices involve maintaining low inventories at the end of the year or quarter to maximize the company's performance for financial statements. The practice of maintaining low inventories is widespread, especially in the case of the more expensive medications.

- ✓ Distribution restriction practices

Exclusive agreements between supply-chain entities (manufacturers, distributors, chain or brand pharmacies) can spark secondary shortages, delaying the declaration of an actual shortage and the communication of information.

- ✓ Stockpiling and absence of control mechanisms

The absence of control measures on quantities sold may also generate artificial shortages. When the price for a particular product goes up, some distributors order larger quantities, thus cutting off the supply for other clients. Rumours of a possible shortage may lead some pharmacists or pharmacy departments to stockpile more drugs than usual, creating a secondary shortage.

“ CURRENTLY NO REGULATION EXISTS THAT OBLIGES THE INDUSTRY TO GIVE ADVANCE NOTIFICATION OF DRUG PRODUCT DISCONTINUATION OR AN ANTICIPATED INTERRUPTION OF THE SUPPLY. ”

¹⁵
See note 14.

The vulnerability of raw material production sites to natural disasters or political unrest

As already mentioned, since the number of raw material producing countries is limited, and many drug manufacturers source these materials from the same suppliers, when facilities are forced to close due to natural disasters or political unrest, the impact on drug production is significant.

Protamine, an antidote to heparin, is currently unavailable around the world due to the 2011 tsunami in Japan, its principal producer.

SERIOUS CONSEQUENCES

Because shortages are more numerous, of longer duration and involve drugs needed to treat critical conditions, impacts have quadrupled.¹⁶

Impact on health

It could be said that, at this point, patients have not been overly affected by drug shortages. Unfortunately, health professionals are increasingly unable to source alternative therapies.

The literature has little to say on this subject. But an ISMP survey conducted in the United States¹⁷ reports deaths and several other impacts of the shortages.

The following impacts were reported:

- ✓ Death;
- ✓ Hospitalizations and longer hospital stays;
- ✓ Progression of the disease, or development of new health problems associated either with halted administration of the drug in shortage, or the diminished effectiveness of alternative therapy;
- ✓ Infections linked to sterility issues of substitute medications when they are compounded in pharmacies or care units under conditions that do not comply with the highest drug manufacturing standards (for example, the USP 797 standard);
- ✓ Loss of control over symptoms due to a less effective pharmacological therapy;
- ✓ Side effects linked to a substitute medication that the patient has difficulty tolerating

The impacts presented above are happening now. A review of industry reports and interviews with 20 experts conducted by the Associated Press in September 2011 show that at least 15 deaths had occurred in as many months in the United States due to drug supply disruptions. In some cases, the deaths were said to have been caused by the absence of a substitute drug, errors in the dosage regime or the administration of substitute drugs.

In 2011, a shortage of CaelyxTM, a drug used in the treatment of ovarian cancer, forced Quebec hospitals to give priority to patients who had already begun treatment over those whose treatment was scheduled to commence in the next few days.

¹⁶ American Society of Health-System Pharmacists & al. Note 11.

¹⁷ «Institute for Safe Medication Practices Drug shortages: National survey reveals high level of frustration, low level of safety. ISMP Medication Safety Alert!», 23 September 2010. Available online at: www.ismp.org/Newsletters/actuecare/article/20100923.asp

Impacts linked to quality and accessibility of care and services

Shortages have adverse repercussions on the quality and accessibility of care and services:

- ✓ Compromise or postponing of a medical or surgical intervention;
- ✓ Adverse responses linked to the substitute drug;
- ✓ Violation, change, delay or compromise of research protocols;
- ✓ Patients forced to go to several pharmacies for the required drug, leading to a dispersal of information on their medication history and increasing their exposure to adverse drug interactions;
- ✓ Generation of secondary shortages due to the creation of contingency inventories and increased demand.

Certain impacts can be unexpected. In September 2011, it was learned that over 150 research protocols of the National Cancer Institute in the US involved the use of a drug that had been in shortage.¹⁸ A disruption in the supply of a drug being used in a research protocol can actually jeopardize the study, which is a real concern in that such studies are costly and are conducted over several years.

An ISMP survey of 1,800 US health practitioners between July and September 2010 revealed that 35% of the respondents believed they had witnessed a “near miss” medication error caused by a drug shortage in their health institution over the preceding year. Some 25% reported actual errors and 20% reported adverse patient outcomes. Physicians were more numerous in reporting accidents with consequences (33%), followed by pharmacists (21%) and nurses (16%).¹⁹

In February 2012, hospitals in Hull and Gatineau, Quebec, were forced to postpone 65 elective surgeries due to anticipated shortages in order to preserve stocks of injectable drugs required for emergencies.

“ IN 2011, A SHORTAGE OF CAELYX™, A DRUG USED IN THE TREATMENT OF OVARIAN CANCER, FORCED QUEBEC HOSPITALS TO GIVE PRIORITY TO PATIENTS WHO HAD ALREADY BEGUN TREATMENT OVER THOSE WHOSE TREATMENT WAS SCHEDULED TO COMMENCE IN THE NEXT FEW DAYS. ”

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Testimony of Charles Penley, «Examining the Increase in Drug Shortages,» before the Committee on Energy and Commerce, 23 September 2011.

19

Kaakeh, R., Sweet, B.V., Reilly, C., and others. Impact of Drug Shortages on US Health Systems. *Am J Health-Syst Pharm.* 2011; 68 (19):1811-9.

Financial impacts²⁰

Shortages mean increased resources are needed and with them higher costs. For example:

- ✓ The generally higher cost of the drugs used to replace the regular treatment (except when a clause negotiated by a purchase group requires the manufacturer to pay the difference);
- ✓ Cost of drugs purchased outside of supply agreements, and emergency shipping costs;
- ✓ Time invested in monitoring available inventory, searching for alternate solutions and associated clinical follow-up;
- ✓ Time invested in preparing a new formulation when alternative solutions are unavailable;
- ✓ Costs of necessary additional therapies;
- ✓ Medical visits required before changing therapy or to assess negative side effects of a new therapy;
- ✓ Time required to implement changes in the automatic distribution system for labelling, packaging and storage of new products, and to train personnel;
- ✓ Costs of postponing surgery or a medical intervention;
- ✓ Costs of management and compensation related to accidents and treatment delays.

According to a poll of ASHP members,²¹ pharmacists and pharmacy technical assistants are the practitioners most affected by drug shortages. The polled hospitals reported that, on average, pharmacists spend nine hours per week managing shortages, pharmacy technical assistants spend eight hours per week, physicians spend 0.5 hours, and nurses, a little less. This survey estimates labour costs of \$216 million are incurred annually in the United States. If the cost differential of substitute drugs is added to the additional labour cost, this represents a minimum of \$415 million incurred by the US health system.²²

²⁰

See note 19.

²¹

See note 19.

²²

Testimony of Mike Alkire, Chief Operating Officer, Premier Healthcare Alliance, on «Examining the Increase in Drug Shortages,» before the Committee on Energy and Commerce Subcommittee on Health. US House of Representatives, 23 September 2011.

Impacts on interprofessional relations and ethical issues

Drug supply disruptions undermine patient-pharmacist relations and physician-pharmacist relations. Roughly 55% of the ISMP survey respondents mentioned that physicians were angry with pharmacists, nurses and hospitals.²³ This situation also raises ethical concerns, with practitioners having to account to the public for their choices. What patients or pathologies are at the top of the list to receive the best drug product that is currently in shortage?

**“ A DISRUPTION
IN THE SUPPLY OF A
DRUG BEING USED IN A
RESEARCH PROTOCOL
CAN ACTUALLY
JEOPARDIZE THE
STUDY, WHICH IS A
REAL CONCERN IN
THAT SUCH STUDIES
ARE COSTLY AND ARE
CONDUCTED OVER
SEVERAL YEARS. ”**

²³
See note 19.



RECOMMENDATIONS OF THE WORKING COMMITTEE

The foregoing underscores the importance of prompt action to reduce the number of drug shortages in Quebec, and, when they are unpreventable, to minimize their impact. Lack of action would translate into serious consequences, both for patients and for the health system as a whole.

The committee reviewed solutions that have been proposed in Great Britain, France, United States, across Canada and in Quebec. Committee members analyzed the advantages and risks of each recommendation, its main impacts and the parties most likely to benefit or suffer.

The Working Committee firmly believes that patients are the principal victims of drug shortages. Any solution that can mitigate or prevent a drug shortage will help to lessen the consequences for patients. From this perspective, it is obvious that solutions will depend on concerted action by all stakeholders. Moreover, the committee's view is that a number of the recommendations must be fast-tracked to ensure the supply of drugs considered to be medically necessary.

Here are the solutions considered by the Committee as the ones most likely to achieve the objectives.



RECOMMENDATION 1

THAT FEDERAL, PROVINCIAL AND TERRITORIAL HEALTH MINISTERS DEVELOP A NATIONAL VISION AND ACTION PLAN TO ENSURE ACCESS TO MEDICALLY NECESSARY DRUGS.

In Canada, provincial governments are responsible for the administration of health-care; drug licensing decisions, however, are made at the federal level. In this, the federal government is guided by a set of policies and decisions, some of which come from the provincial health ministers.

Clearly, the Conference of Ministers of Health needs to adopt some fundamental principles to ensure access to medically necessary drugs for Canadians.

A recent WHO bulletin states that “Access to essential medicines is well founded in international law as part of the right to the highest attainable standard of health (“the right to health”). The *International Covenant on Economic, Social and Cultural Rights* adopted in 1966 calls for States Parties to take steps to ensure access to medical services for all. General Comment 14, added in 2000, applies the principles of accessibility, availability, appropriateness and assured quality to goods and services, including essential medicines as defined by the World Health Organization (WHO) Action Programme on Essential Drugs.”²⁴

It is the role of government to reset the priorities guiding healthcare stakeholders. Current government policies, laws and standards governing supply-chain entities have proven to be ineffective in ensuring the primacy of patients’ needs.

How to achieve this

Efforts should be initiated quickly to develop a national vision concerning the supply of drug products. This vision should determine which drugs are medically necessary, and its associated action plan should include measures to guarantee a stable and adequate supply across the country.

Moreover, the adoption of guiding principles for the development of good drug supply management practices will enable supply-chain entities to strictly manage the supply of medicines and maintain the integrity of the chain. Organizations such as the International Pharmaceutical Federation have a role to play in the development of these guiding principles.

Implement a communications strategy to sensitize stakeholders who can positively influence the development of such a vision. The *Ordre des pharmaciens du Québec*, with the support of this report’s signing organizations, is ready to initiate this discussion.

“ CLEARLY, THE
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MINISTERS OF HEALTH
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SOME FUNDAMENTAL
PRINCIPLES TO ENSURE
ACCESS TO MEDICALLY
NECESSARY DRUGS
FOR CANADIANS. ”

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Bulletin of the World Health Organization, 2010;88:800-800. Reference: Hestermeyer, HP. *Access to Medication as a Human Right*. Max Planck UNYB 8 (2004), page 128.

RECOMMENDATION 2

THAT HEALTH CANADA ADAPT ITS REGULATIONS AND PROGRAMS TO ADDRESS SHORTAGES.

Regulations are always slow to adapt to environmental changes. Federal Minister of Health Leona Aglukkaq initiated a task force made up of Canadian industry representatives and professional associations that set up two websites for the reporting of information related to drug shortages. Information is provided by manufacturers on a voluntary basis.²⁵ Other than this measure, however, no significant changes have been made to Health Canada's programs.

Drugs, like water, are exceptional consumer products that merit specially tailored controls. The Working Committee proposes the following changes.

Enhance oversight of industry practices

- ✓ Manufacturers' decisions concerning drug discontinuations, halts in production or manufacturing site closures should be submitted to an entity for preliminary approval based on a risk/benefit analysis. If no other manufacturer is able to produce the drug, or if such a transfer would entail too much risk, Health Canada should have the power to refuse the production stoppage or postpone the manufacturing site closure (see also Recommendation No. 4).
- ✓ Require manufacturers to diligently report any situation likely to affect supply.
In the United States, an average of 10 notifications were received monthly in the months preceding the Obama administration's efforts to increase the FDA's powers.²⁶ The agency now receives 61 notifications per month. The draft legislation, *Preserving Access to Life-Saving Medication Act*, requires manufacturers to notify the FDA of anticipated shortages. Failure to provide notification could result in maximum penalties of \$10,000 per day or a total of \$1.8 million.
- ✓ Require manufacturers submitting Notice of Compliance applications to provide information on anticipated demand and prove their ability to guarantee stable production, specifically, by presenting a risk management plan for shortages.
- ✓ Require manufacturers applying for approval of a medically necessary or single-source drug to provide several sources for active ingredients and several manufacturing sites.

“ DRUGS, LIKE WATER, ARE EXCEPTIONAL CONSUMER PRODUCTS THAT MERIT SPECIALLY TAILORED CONTROLS. ”

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The sites in question are *VendrediPM* (www.vendredipm.ca), the English equivalent *FridayPM* (www.fridaypm.ca) and the site of the Saskatchewan Drug Information Services: http://druginfo.usask.ca/healthcare_professional/drug_shortages.php Databases are also provided by Canadian Pharmaceutical-based Research Companies at: <https://www.canadapharma.org/shortage/index.asp> and by the CGPA at www.canadiangenerics.ca/en/advocacy/shortages.asp

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Testimony of Sandra Kweder, M.D. Deputy Director, Office of New Drugs Center for Drug Evaluation and Research. Food and Drug Administration Department of Health and Human Services before the Committee on Health, Education, Labor and Pensions. United States Senate. «Prescription Drug Shortages: Examining a Public Health Concern and Potential Solution,» 15 December 2011, pages 12-13.

“ IN THE UNITED STATES, AN AVERAGE OF 10 NOTIFICATIONS WERE RECEIVED MONTHLY IN THE MONTHS PRECEDING THE OBAMA ADMINISTRATION’S EFFORTS TO INCREASE THE FDA’S POWERS. THE AGENCY NOW RECEIVES 61 NOTIFICATIONS PER MONTH. ”

That Health Canada review some of its practices

- ✓ Shorten the waiting period for decisions on change requests (e.g., change of manufacturing protocol or raw material supplier). Currently, the waiting period in Canada is eight to 12 months.
- ✓ For drugs in shortage or potentially in shortage, expedite approval processes (for a change or licence). Provide support to manufacturers to accelerate decision-making processes.
- ✓ Harmonize certain Health Canada and FDA regulatory processes, in particular, inspections and approvals of change requests (an agreement between President Obama and Prime Minister Harper signed in 2011 could represent the beginning of such harmonization).²⁷
- ✓ Provide incentives to manufacturers of licensed drugs to source secondary suppliers of key components, particularly the active ingredients needed in drug production.
- ✓ Establish intergovernmental regulations (federal and provincial) to ensure strict control of the supply-chain according to the respective jurisdictions of different levels of government (e.g., require notifications or the signing of an agreement with a manufacturer who can guarantee production, etc.).
- ✓ When quality-control systems note minor manufacturing defects in certain drugs, allow controls to be relaxed on these batches of drugs if they are short supply, after conducting additional evaluations and providing health practitioners with special notices. For example, a batch of medication was released after an analysis showed that it could be safely administered with the use of a filter. This defective batch was accompanied by a notice specifically addressed to health practitioners.

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www.cbc.ca/news/politics/story/2011/12/07/pol-canada-us-border-perimeter.html

Review Health Canada's Special Access Programme in Light of Shortages.

- ✓ Under the Special Access Programme, a drug can be imported for a patient with a specific need (e.g., when treatment is unavailable in the country or the patient is allergic to the available therapy). Currently, the program may be applied to only one patient at a time. Because of the shortages, it must be applied to many patients. The Committee therefore recommends a review of the Special Access Programme to ensure that:
 - it responds more effectively and quickly to high-volume demands involving the substitution of medically necessary medicines in shortage;
 - practitioners obtain help to locate additional supply sources;
 - it allows for the delivery of medicines to private-practice pharmacists (currently, only health institutions and physicians are eligible to receive the drugs).

Other methods

- ✓ Review manufacturing requirements and set up a program to license pharmacies to produce drugs that are in shortage.

“ UNDER THE SPECIAL ACCESS PROGRAMME, A DRUG CAN BE IMPORTED FOR A PATIENT WITH A SPECIFIC NEED. BECAUSE OF THE SHORTAGES, IT MUST BE APPLIED TO MANY PATIENTS. ”

RECOMMENDATION 3

THAT MANUFACTURERS ADOPT RESPONSIBLE INVENTORY MANAGEMENT PRACTICES AND ETHICAL PRACTICES IN SITUATIONS OF SHORTAGES.

Manufacturers play a major role in the prevention and management of supply disruptions.

In terms of prevention, internal procedures must be implemented for the tracking, avoidance and correction of shortages. The systematic introduction of redundancies in critical manufacturing processes for medically necessary or single-source drugs must be implemented.

Standardize practices such as the maintenance of adequate inventories to meet demand for a defined period. Also, manufacturers must plan for quick intervention in the event of a shortage. A contact person appointed by every manufacturer should notify the coordinating entity of an anticipated shortage, its severity, duration, substitute therapies, proposed solutions, and the general contingency plan.

In addition, manufacturers should analyze the causes of prolonged shortages of medicines they manufacture and produce a report for the coordinating entity that presents the highlights of this analysis.

Of primary importance: a secondary raw material supplier should be available for all medically necessary drugs. Production priorities should be determined based on the needs of the population.

Industry codes of ethics must address the phenomenon of shortages. For instance, they should support the coordinating entity's role and could also require notification of quality issues (non-compliant batches), anticipated or current shortages.

Industry must act responsibly. Practices such as increasing the price of substitute drugs during a shortage must be publicly condemned by manufacturer associations. Under no circumstances should the desire to protect the market for a drug prevail over patients' access to medically necessary drugs.

OF PRIMARY IMPORTANCE: A SECONDARY RAW MATERIAL SUPPLIER SHOULD BE AVAILABLE FOR ALL MEDICALLY NECESSARY DRUGS. PRODUCTION PRIORITIES SHOULD BE DETERMINED BASED ON THE NEEDS OF THE POPULATION.

RECOMMENDATION 4

THAT LEGISLATION BE PASSED REQUIRING MANUFACTURERS TO PROVIDE ONE YEAR'S ADVANCE NOTICE BEFORE THE VOLUNTARY DISCONTINUATION OF A DRUG. THE MANUFACTURER WOULD HAVE TO WAIT FOR APPROVAL BEFORE HALTING PRODUCTION OF A MEDICALLY NECESSARY OR SINGLE-SOURCE DRUG.

Several countries already require manufacturers to provide advance notice of the permanent or partial discontinuation of a drug. In France, manufacturers must announce their intention to discontinue a production line one year in advance, and they must await approval from the authorities before doing so.²⁸ The European Union requires two-month advance notice before temporary or permanent production stoppages.²⁹

A U.S. bill aims to oblige manufacturers to provide notification of any production stoppages. In the case of a permanent discontinuation, notice would have to be given six months in advance.

If Canadian law obliged manufacturers to provide such advance notification to provincial and federal authorities, it would then be possible to implement alternative solutions. For example, if necessary, production could be transferred to another manufacturer.

For medically necessary and single-source drugs, authorities should be able to intervene to prevent a drug from being permanently discontinued when prior authorization has not been obtained. This would allow for earlier detection of market concentration and drugs at risk of being produced by a single manufacturer.

“ SEVERAL COUNTRIES ALREADY REQUIRE MANUFACTURERS TO PROVIDE ADVANCE NOTICE OF THE PERMANENT OR PARTIAL DISCONTINUATION OF A DRUG. IN FRANCE, MANUFACTURERS MUST ANNOUNCE THEIR INTENTION TO DISCONTINUE A PRODUCTION LINE ONE YEAR IN ADVANCE, AND THEY MUST AWAIT APPROVAL FROM THE AUTHORITIES BEFORE DOING SO. ”

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Legislation passed on 29 December 2011 to reinforce the security of drugs and health products, article L5421-8. Available online at: http://www.legifrance.gouv.fr/affichCode.do;jsessionid=A519B002428803B6A91B9431FADB786E.tpdjo10v_3?cidTexte=LEGITEXT000006072665&dateTexte=20120328

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See Note 6.

RECOMMENDATION 5

THAT PROVINCIAL HEALTH MINISTER DESIGNATE AN ENTITY TO COORDINATE THE MANAGEMENT OF SHORTAGES AND NECESSARY INFORMATION ON DRUG SHORTAGES.

“ IN FRANCE, A GOVERNMENT AGENCY PERFORMS A ROLE SIMILAR TO WHAT WE ARE PROPOSING HERE. IN THE UNITED STATES, THE FDA ACTS AS THE COORDINATING ENTITY. THE DRUG SHORTAGES PROGRAM SUCCEEDED IN PREVENTING 38 SHORTAGES IN 2010, 195 SHORTAGES IN 2011, AND 18 SHORTAGES AS OF 9 FEBRUARY 2012. ”

This recommendation must be prioritized because it will make it possible, in the near and medium term, to prevent certain shortages and prioritize a patient-centred response.

In France, a government agency performs a role similar to what we are proposing here. In the United States, the FDA acts as the coordinating entity. The Drug Shortages Program succeeded in preventing 38 shortages in 2010, 195 shortages in 2011, and 18 shortages as of 9 February 2012.³⁰

The FDA affirms that this success is due to the implementation of early disclosure by manufacturers. Under an Executive Order issued by President Obama³¹, manufacturers are obliged to report on manufacturing issues that could disrupt the supply of a medically necessary drug or treatment for a disabling condition. Before, they were only required to give notice of a product discontinuation.

The same Executive Order also calls on the FDA to expedite regulatory processes to avoid new shortages and mitigate the impact of those already underway. Further, the FDA must notify the Minister of Justice when companies take advantage of a shortage, for instance, with price gouging. Additional employees were allocated to manage shortages (six employees were added to the existing staff of four).

Among the most common actions of the FDA³²:

- ✓ With respect to shortage prevention:
 - Accelerate inspection process and assessments of new manufacturing sites, new suppliers and change requests (71%)
 - Flexibility through regulatory discretion (20%), for example, quickly releasing batches after analysis, accompanied by notices to health practitioners
 - Asking other manufacturers to produce drugs in shortage (7%)

³⁰ CDR Emily Thakur, R.Ph., *US Public Health Service Drug Shortage Program*, Center for Drug Evaluation & Research, US Food and Drug Administration. Presentation on 9 February 2012.

³¹ Fact Sheet *Obama Administration Takes Action to Reduce Prescription Drug Shortages in the US*, The White House, mht.

³² See Note 6.

- ✓ With respect to mitigating shortages
 - Asking other manufacturers to increase their production (31%)
 - Helping manufacturers find ways to minimize quality-related risks in drug manufacturing (28%)
 - Accelerating review of regulatory submissions (26%)

In Quebec, we do not need to create a new organization to assume coordination. Existing agencies that are already involved in the issue could be assigned this role. While such a structure would normally be empowered on a country-wide basis, the Canadian constitutional context defines health as a provincial jurisdiction; provincial governments could therefore empower such an entity. We believe that this body would have to maintain regular contact with the federal government, in particular, Health Canada, and a partnership would need to be developed with the federal authority to ensure the common goal of preventing and minimizing the impact of drug supply disruptions.

Functions of the coordinating entity

This body would have the following functions:

HELP TO PREVENT SHORTAGES:

✓ Receive and assess notifications of anticipated shortages

Since no organization is currently responsible for receiving notifications of anticipated shortages, it is impossible to implement effective measures to prevent or minimize future shortages.

When a shortage is anticipated, for instance, due to a permanent or temporary halt in production or a manufacturing problem, manufacturers must notify the coordinating entity.

This body could then mobilize a group of stakeholders to seek solutions: fast-track approval of substitute drugs, production agreement with another manufacturer, notices to health practitioners to replace their patients' therapy with another available therapy, etc.

Insurers could adapt payment policies in times of shortages and accelerate their application. For example, they could plan in advance for coverage of a substitute drug when a supply disruption of the usual medication is announced.

“ WE BELIEVE THAT THIS BODY WOULD HAVE TO MAINTAIN REGULAR CONTACT WITH THE FEDERAL GOVERNMENT, IN PARTICULAR, HEALTH CANADA, AND A PARTNERSHIP WOULD NEED TO BE DEVELOPED WITH THE FEDERAL AUTHORITY TO ENSURE THE COMMON GOAL OF PREVENTING AND MINIMIZING THE IMPACT OF DRUG SUPPLY DISRUPTIONS. ”

✓ **Identify problem and critical situations and propose actions for their resolution**

Similarly, and to complement the notification of anticipated shortages, manufacturers should regularly report drugs for which quantities are below the minimum supply period that is based on predetermined criteria, and explain the reasons for the expected supply disruption. This would facilitate the advance targeting of critical situations.

The coordinating entity would then be informed of the causes for decreased inventory and, here again, be able to adopt prevention measures.

INTERVENE IN THE EVENT OF A SHORTAGE OR WHEN A SHORTAGE IS FORTHCOMING:

✓ **Implement contingency measures and inform supply-chain stakeholders**

Each supply-chain stakeholder should have a contingency plan. The coordinating entity would be responsible for ensuring that this has been done and would oversee harmonization of these plans. A national contingency plan should also be put in place. In addition to developing such a plan, the entity would be responsible for establishing criteria governing the plan's implementation. Among other elements, this plan should specify that in the event of a serious shortage of one or more products, the coordinating entity, not the manufacturer, would be responsible for overseeing the actions to be undertaken in such situations. Contingency plans should consider the fact that resupplying the whole chain takes from two to three months.

In the event of a shortage, the coordinating entity's mandate would be to inform all supply-chain stakeholders of the actions that have been taken.

Contingency plans should be developed across the pharmacy supply-chain. The British Department of Health has set guidelines defining the roles and responsibility of supply-chain entities and providing useful elements for a future national contingency plan.

✓ **Determine what information must be collated and ensure its management**

The coordinating entity should set up a unit composed of clinical and operation management experts who would determine criteria that would set in motion a review of the situation to validate, analyze and monitor indicators.

This unit would identify the information that should be collated in the event of a shortage, and ensure its management. The coordinating entity would collate information on the nature of the drug in short supply (medically necessary or not), duration of the shortage, available inventory, expected date of return to the market, etc.³³

The coordinating entity would therefore be a key player in the event of a drug supply disruption: a centralized information centre and coordinating body. In this, it would be advised by a team of experts.

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The Working Committee has produced a list of information to be collated by the coordinating entity. It is included in Appendix 2.

✓ **Make information available to health practitioners**

Information systems already exist but they are incomplete or are not updated in real time, which impedes the effective management of shortages. A major irritant is the fact that many practitioners end up spending time searching for the same information in isolation.

The Committee believes that the coordinating body should centralize all information for health practitioners in one location.³⁴

A more comprehensive and transparent information system would allow pharmacists to respond proactively when a shortage is declared.

✓ **When needed, create expert groups to resolve more complex situations**

In complex situations, clinical expert groups could be created to find alternative therapies to the drugs in shortage. In addition to proposing alternative treatments, these experts could identify priority patient categories. The same mechanism could be applied to quickly establish the procedure to be followed in complex situations.

These experts could also approve exceptional measures for managing residual inventories and ensuring the safe application of any changes deemed necessary in the medication circuit.

✓ **Promote and enforce the compliance of supply-chain stakeholders with good management practices for the supply of drug products**

If they do not exist already, the coordinating entity could adopt good practices for the supply of drug products and publish a reference document for the use of supply-chain stakeholders.

The coordinating entity would be assigned to perform these activities and prioritize medically necessary drugs. To this end, it should maintain an updated list of medically necessary drugs, adapted to the needs of Canadians, and based on the list published by the World Health Organization. At this time, there is no distinction between the supply of regular drugs and the supply of medically necessary drugs; and the distribution of pharmaceutical products is not always adequate to meet priority needs. Contingency measures must prioritize drugs deemed medically necessary.³⁵

“ INFORMATION SYSTEMS ALREADY EXIST BUT THEY ARE INCOMPLETE OR ARE NOT UPDATED IN REAL TIME, WHICH IMPEDES THE EFFECTIVE MANAGEMENT OF SHORTAGES (...) MANY PRACTITIONERS END UP SPENDING TIME SEARCHING FOR THE SAME INFORMATION IN ISOLATION. ”

“ AT THIS TIME, THERE IS NO DISTINCTION BETWEEN THE SUPPLY OF REGULAR DRUGS AND THE SUPPLY OF MEDICALLY NECESSARY DRUGS; AND THE DISTRIBUTION OF PHARMACEUTICAL PRODUCTS IS NOT ALWAYS ADEQUATE TO MEET PRIORITY NEEDS. CONTINGENCY MEASURES MUST PRIORITIZE DRUGS DEEMED MEDICALLY NECESSARY. ”

³⁴ See list of items to be included in these information system in Appendix 3.

³⁵ See definition on page 12.

RECOMMENDATION 6

THAT FEDERAL AND PROVINCIAL GOVERNMENT POLICY INCLUDE INCENTIVES TO PRODUCE MEDICINES IN SHORTAGE AND DRUGS WITH LOWER PROFIT MARGINS.

Current bidding and price-setting systems establish such low prices for some drugs as to threaten their commercial viability.

The Committee therefore recommends:

- ✓ Implementation of a price review procedure that acknowledges the actual costs involved in manufacturing older, more affordable drugs and the complexity of manufacturing processes. Medicines meeting specific criteria would be subject to such a review:
 - single-source drugs;
 - two-source drugs that have been marketed for over 20 years;
 - two-source drugs with annual sales less than \$2 million (for example).
- ✓ Conclude agreements with manufacturers to guarantee stable production of medically necessary or single-source drugs.
- ✓ Create incentives for new or existing manufacturers to produce drugs in shortage and single-source drugs (e.g., guarantee an exclusive-production period).
- ✓ Create incentives to ensure production continuity by manufacturers of products vulnerable to discontinuation following price drops.
- ✓ Plan for agreements with manufacturers to ensure production of drugs that are highly vulnerable to shortages.
- ✓ Provide incentives to support the adoption of excellent practices for manufacturing and improving manufacturing facilities for medically necessary and single-source drugs with a view to increasing production capacity.
- ✓ Provide incentives to manufacturers who are willing to set up new production lines and produce, on demand, drugs in shortage and drugs vulnerable to shortages.
- ✓ Provide incentives for manufacturers with good records of uninterrupted production.

The Committee believes it would be useful to assess the pertinence of a Crown corporation supplying residual production capacity. The evaluation must consider the merits and risks of such an enterprise, and the fact that it can take five to seven years to build a new manufacturing site.

“ THE COMMITTEE
THEREFORE
RECOMMENDS:
IMPLEMENTATION
OF A PRICE REVIEW
PROCEDURE THAT
ACKNOWLEDGES THE
ACTUAL COSTS INVOLVED
IN MANUFACTURING
OLDER, MORE
AFFORDABLE DRUGS
AND THE COMPLEXITY
OF MANUFACTURING
PROCESSES. ”

RECOMMENDATION 7

THAT PURCHASE CONTRACTS AND REFUND AGREEMENTS INCLUDE INCENTIVES FOR GUARANTEED SUPPLY AND PENALIZE SUPPLY DISRUPTIONS.

Purchasing groups that supply drugs to health institutions buy millions of dollars' worth of drugs every year. In Quebec, the biggest purchaser of drugs is the RAMQ. The volume of their purchases empowers these organizations to propose incentives and penalties, depending on the situation. Some contracts already contain such measures, but the practice should be systematized; incentives and penalties should be substantial enough to bring about a change in behaviour.

For example, here are some clauses or requirements recommended by contract managers:

- ✓ Compulsory participation in the drug shortage information system;
- ✓ Prompt notification of a potential supply disruption;
- ✓ Upon signing a contract, submission of a contingency plan for drugs vulnerable to supply disruptions;
- ✓ Commitment to maintaining adequate inventories to supply the market defined by the agreement for a given period;
- ✓ Creation of a guaranteed inventory of medically necessary drugs for the duration of the contract;
- ✓ Recourse to a previously designated manufacturer in the event of a shortage;
- ✓ Penalties in the event of a shortage when there is no alternative solution;
- ✓ Payment of the difference between the prices of contracted and substitute drugs;
- ✓ Penalties for additional expenses incurred during shortages.

“ THE VOLUME OF THEIR PURCHASES EMPOWERS THESE ORGANIZATIONS TO PROPOSE INCENTIVES AND PENALTIES, DEPENDING ON THE SITUATION. SOME CONTRACTS ALREADY CONTAIN SUCH MEASURES, BUT THE PRACTICE SHOULD BE SYSTEMATIZED; INCENTIVES AND PENALTIES SHOULD BE SUBSTANTIAL ENOUGH TO BRING ABOUT A CHANGE IN BEHAVIOUR. ”

Conversely, contracts could:

- ✓ Guarantee a set purchasing volume;
- ✓ Offer longer-term contracts for generic medications that have been marketed for a long time (older generics);
- ✓ Allow prices for older generic medications to be increased without having to break the contract;
- ✓ Explore methods of avoiding recourse to a single supplier, especially when a large purchasing group is supplying drugs to several regions.

Enhanced monitoring could also be planned for repeat tender calls. Currently, under certain circumstances, purchasers are allowed to reissue a tender call while the contract is in effect. This makes it harder for manufacturers to accurately forecast needs and plan accordingly.

During tender calls, drug purchasers should consider past supply disruptions when evaluating bidders.

RECOMMENDATION 8

THAT DISTRIBUTORS ADOPT DISTRIBUTION AND INVENTORY MANAGEMENT PRACTICES THAT GUARANTEE THE SAFETY OF THE SUPPLY-CHAIN AND ENSURE RESILIENCY IN RESPONDING TO URGENT OR PRIORITY NEEDS.

In addition to the manufacturers and government authorities, other drug supply-chain stakeholders, such as distributors and pharmacists, have a role to play in preventing shortages.

The Committee believes that distributors should adopt the following practices:

In a shortage:

- ✓ Notify the coordinating entity as soon as they note a slowdown or disruption in their supply.
- ✓ Share surplus inventory of drugs in shortage with other distributors (based on defined criteria);
- ✓ Refrain from giving priority to certain pharmacists, pharmacy chains, or institutions.
- ✓ At the request of the coordinating entity, redistribute any medically necessary drugs that are still available to pharmacies serving patients requiring ongoing treatment with those drugs;
- ✓ Apply fair distribution measures to clients based on the date and nature of their demand, purchasing history, and quantities available.

In general:

- ✓ Do not sell a drug outside the province or country without notifying the coordinating entity;
- ✓ Sign agreements with clients specifying second-choice drugs for delivery in the event of a supply disruption of the ordered drugs;
- ✓ Do not stockpile drugs other than those required to meet existing needs;
- ✓ Ensure a guaranteed inventory of medically necessary drugs;
- ✓ Develop and apply a contingency plan to effectively intervene in the event of a shortage. Each distributor should designate a representative that will notify the coordinating entity about all the drugs it distributes as soon as it is faced with a supply disruption.

“ THE COMMITTEE BELIEVES THAT DISTRIBUTORS SHOULD SHARE SURPLUS INVENTORY OF DRUGS IN SHORTAGE WITH OTHER DISTRIBUTORS (BASED ON DEFINED CRITERIA) ”

RECOMMENDATION 9

THAT PHARMACISTS RESPONSIBLY MANAGE THEIR DRUG SUPPLY AND FACILITATE THE EQUITABLE USAGE OF AVAILABLE MEDICINES.

Pharmacists have a professional responsibility. They should not create or exacerbate an existing or anticipated shortage, for example, by hoarding more drugs than are needed to meet regular needs. Moreover, they should always order from authorized suppliers and uphold the integrity of the supply-chain. The recourse to unapproved suppliers, for example, Internet suppliers, is prohibited under all circumstances.

The Ordre des pharmaciens du Québec undertakes to clearly communicate the responsibilities of pharmacists to ensure the safe management of the drug supply. Further, the Order will specifically describe actions contrary to the honour and dignity of the profession. For example, it would be unacceptable for a pharmacist to benefit from a partial shortage as a competitive advantage. The Order will also promote good drug-supply management practices once these have been agreed upon. A public reminder will be issued to the effect that pharmacists should be selected based on the quality of their services rather than on the availability of a drug. This is why pharmacists must share inventory in the event of a drug shortage.

The Committee believes that pharmacists should adopt the following practices:

In a shortage:

- ✓ Ration quantities of dispensed drugs, and, in conjunction with physicians, identify priority patients;
- ✓ Share drugs that are in short supply with other pharmacists or pharmacy departments to ensure accessibility and treatment continuity required by patients.
- ✓ Share all information relating to the management of shortages (available inventory, compounded mixtures, stability, etc.).

In general:

- ✓ Develop a contingency plan to effectively intervene in the event of a shortage;
- ✓ Identify a second-choice manufacturer with the distributor;
- ✓ Establish an agreement containing at least two different sources for medically necessary drugs;
- ✓ In partnership with physicians, develop group prescriptions that can be applied in the case of drugs most frequently affected by shortages;
- ✓ In situations of complete supply disruptions in Quebec, replace the prescribed drug with another drug in the same therapeutic sub-class, following the conditions and terms determined by regulation.

“ THE ORDRE DES PHARMACIENS DU QUÉBEC UNDERTAKES TO CLEARLY COMMUNICATE THE RESPONSIBILITIES OF PHARMACISTS TO ENSURE THE SAFE MANAGEMENT OF THE DRUG SUPPLY. ”

CONCLUSION

Drugs are the most powerful therapeutic tools currently employed by health practitioners. They are the focus of exceptional research dedicated to improving health and saving patients' lives.

It is important to keep in mind, however, that pharmaceuticals are at the centre of major economic concerns involving countless global shareholders. This is a huge market, and many people view drugs just as they would any other consumer product. Their unique character with respect to health gives them a special status that up to now has not been sufficiently regulated. A new response is required. The diminishing offer of drugs—until now, a rare event—has become a reality, and economic priorities could drive decisions, for instance, to prioritize the production of certain drugs at the expense of other, less profitable drugs. The concentration of raw material in only a few countries is another cause for concern and makes the whole planet more vulnerable to shortages. The World Health Organization and the International Monetary Fund must consider measures to enhance access and promote the appropriate usage of drug products. Our report refers to a number of these factors, but at this time is only proposing solutions for implementation at the national, provincial and local levels.

Already, a year has gone by in which the Ordre des pharmaciens du Québec, Collège des médecins du Québec, Association des pharmaciens en établissement de santé, and Association québécoise des pharmaciens propriétaires have devoted themselves to this issue because they believe it is crucial for the protection of the public. Recent experiences in Quebec and elsewhere in Canada have highlighted the urgent need for a planned response, rather than improvised and isolated actions that will only generate increased vulnerability. Quick implementation of the proposed oversight mechanism is imperative.

Repeated supply disruptions, especially those affecting medically necessary drugs, place patients, society in general, and health practitioners in extremely difficult clinical, ethical and economic circumstances. The Working Committee hopes that this report will convince people of the scope and gravity of the problem, and especially, of the urgent need for prompt action.

In the interest of all patients in Quebec, it is crucial that all stakeholders collaborate to avoid these shortages. Management practices must be improved and health practitioners empowered to deal with shortages when they cannot be prevented. All levels of government must act to prevent the root causes of shortages. Manufacturers must act more responsibly with regard to the essential goods they are producing. The organizations presenting this report will make every effort in the upcoming months to ensure that the different levels of government and other stakeholders capable of acting on this issue work to implement these recommendations.

Our work can serve as the basis for new strategies. Moreover, we hope that the Committee's work will contribute to knowledge sharing about drug shortages throughout Quebec's health system and thereby help to protect the public.

We hope this report will result in the public being better informed about the issue and empowered to convince decision-makers and concerned parties to devote the proper attention to addressing it.

APPENDIX 1

DESCRIPTION OF THE SUPPLY PROCESS AND SUPPLY-CHAIN ENTITIES³⁶

Raw material production: Raw material manufacturers are responsible for raw materials production and packaging. Distributors are responsible for distribution.

Drug production: Manufacturers produce drug products. They manufacture them out of raw materials and other components, and then process, package and ship them to the distributors, or, in some cases, directly to pharmacies or health institutions. Ideally, the quantities produced would be equal to the quantities demanded (prescribed). Manufacturers influence prescription habits through scientific publications, and promotional and marketing activities addressed to prescribers and consumers. Manufacturers are responsible for the safe use of their products, in particular, with respect to good manufacturing, labelling and traceability practices (use of bar codes).

Wholesale distribution: Distributors purchase drugs from manufacturers and sell them to pharmacies and health institutions. Ideally, they are responsible for their storage and inventory management to meet client needs. Some distributors have diversified their offering and provide specialized drug distribution services (robots, automatic distribution firms, etc.), electronic prescribers and other tools requested by their clientele.

Pharmaceutical services (pharmacies): Pharmacies and health institutions purchase drugs from distributors and occasionally, from manufacturers. They are responsible for supplying medications to patients, as well as drug storage and inventory management. Ideally, they provide patients with sufficient quantities of the drugs they have been prescribed. Pharmacies also facilitate payment and reimbursement processes with the insurers for their patients' medicines.

See the summary diagram on the following page.

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The Health Strategies Consultancy
LLC. *Follow The Pill: Understanding
the US Commercial Pharmaceutical
Supply-chain.* The Henry J. Kaiser Family
Foundation, March 2005.

SUPPLY PROCESS AND SUPPLY-CHAIN ENTITIES

(IN THE LITERATURE, SHORTAGES ARE CONNECTED WITH PRACTICES OF THE DRUG SUPPLY-CHAIN ENTITIES)

RAW MATERIAL PRODUCTION

Insufficient quantities of raw materials and quality issues

DRUG MANUFACTURING

Increased demand, volatility of demand and production
Production stoppages for non-compliance with manufacturing
Production stoppages or delays due to business or economic considerations
Industry mergers and consolidations (manufacturers and distributors)
The vulnerability of raw material production sites to natural disasters or political unrest
Distribution restriction practices
Inventory minimization practices
Absence of legislation and drug shortage-related constraints imposed on manufacturers and distributors

MARKET APPROVAL

Regulatory requirements that complicate the production process
Delays in regulatory decisions and unpredictable turnaround time for processing approval requests
Production stoppages or delays due to changes in manufacturing procedures or transfers of production lines

IDRUG SCHEDULING, PRICING

Production stoppages or delays due to business or economic considerations
Consolidations of purchasing groups, concentrating several regions' purchasing activities in a small group

INSPECTION OF MANUFACTURING SITES

Production stoppages for non-compliance with manufacturing processes and recalls
Foreign regulatory bodies can affect the local supply

WHOLESALE DISTRIBUTION

Distribution restriction practices
Inventory minimization practices
Stockpiling and absence of control mechanisms
Absence of legislation and drug shortage-related constraints imposed on manufacturers and distributors

PHARMACEUTICAL SERVICES (PHARMACIES)

Inventory minimization practices
Stockpiling and absence of control mechanisms

APPENDIX 2

INFORMATION THAT THE COORDINATING ENTITY MUST COLLATE IN THE EVENT OF A SUPPLY DISRUPTION

The coordinating entity should collate and manage specific information in the event of a supply disruption. For example, it could collect the following information:

- ✓ nature of the drug in shortage: whether or not it is medically necessary or the sole therapy;
- ✓ likely duration of shortage;
- ✓ available stock;
- ✓ market share of the drug affected by the supply disruption;
- ✓ purchase volumes;
- ✓ number of companies that manufacture the product;
- ✓ nature and cause of shortage;
- ✓ measures planned for resolving the shortage;
- ✓ manufacturer's internal assessment, to determine production capacity needed to address the shortage;
- ✓ potential of product hoarding by other supply-chain stakeholders.

APPENDIX 3

INFORMATION THAT SHOULD BE INCLUDED IN INFORMATION SYSTEMS USED BY HEALTH PRACTITIONERS

The following information should be circulated among health practitioners:

- ✓ list of drugs in shortage (name and format) and available substitute products;
- ✓ start date of shortage and date of return to the market;
- ✓ manufacturer's name, contact person, telephone and fax numbers, e-mail address;
- ✓ proposed drug procurement procedure. If applicable:
 - List of available back-up drug manufacturers to source the product in shortage with link and telephone number for placing orders;
 - List of distributors that have the product in stock with link and telephone number for placing orders;
 - Billing procedure and other administrative information useful for, among other things, payments for medicines supplied by compounding pharmacists. Link to the notice explaining the billing procedure.
- ✓ When a supply disruption concerns a complex situation, provide a list of available alternative therapies or recognized compounded mixture preparations suggested by the manufacturer and validated by a group of specialists.

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