Drug Shortages: Searching for a Cure

Pénuries de médicaments: À la recherche d'un remède

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Abstract

Shortages of prescription generic drugs have recently made headlines in Canada and elsewhere. The causes and possible solutions for these shortages are still unclear. With the failure of "market forces," has the time come to establish a Crown corporation to ensure the supply of essential drugs?

Résumé

Les pénuries de médicaments génériques ont récemment fait les grands titres au Canada et à l'étranger. Les causes et les solutions possibles à ces pénuries font encore l'objet de débats. Étant donné l'échec des "forces du marché", le temps est-il venu de créer une compagnie publique pour assurer l'approvisionnement en médicaments essentiels?

In recent months, drug supply management, normally considered a boring aspect of healthcare policy, has become an extreme sport for healthcare organizations and practitioners. In February 2012, the company Sandoz, a generic manufacturer owned by Novartis, announced that it had to slow down production of injectables in Quebec in order to comply with quality-control requirements from the US Food and Drug Administration (FDA). After Sandoz flunked a series of inspections, the FDA threatened, in a warning letter dated November 18, 2011, to refuse entry to the United States of Sandoz products manufactured in Quebec.[1]

After slowing its manufacturing operations, Sandoz completely stopped production for a week following a small fire at its Quebec plant, and also recalled products in March because of packaging problems. In the meantime, Canadians realized that Sandoz produces most of all generic injectables in Canada, and was in fact the sole supplier of 140 injectables used by Canadian hospitals, including all forms of injectable morphine. Minor troubles in the adaptation of production to comply with existing quality-control regulations thus quickly transformed into a national catastrophe in the Canadian healthcare sector, forcing the postponement of dozens of surgeries and mobilizing every healthcare organization in the country to find a solution to shortages. An emergency debate took place in Parliament, and the Canadian Generic Pharmaceutical Association (CGPA, the lobby group for generics manufacturers) even teamed up with Rx&D, the lobby group for brand-name pharmaceutical products, to address the issue.[2]

Drug shortages are not a new phenomenon. What is new is that their frequency and duration are escalating at a fast pace.[3] In the United States, recent drug shortages have been described as life-threatening and are considered the worst in 20 years (Morrison 2011).

Drug shortages are always a headache for pharmacists, who try to compound with alternatives, and shortages are often related to an increase in harmful medication errors (Institute for Safe Medication Practices Canada 2012). While drug shortages are rarely reported in the media, the disruption at Sandoz has at least placed the spotlight on this growing concern in the healthcare sector. Discussion of possible solutions is underway, although there is still little consensus over what causes shortages. Some critics blame mergers and restructuring in the global sector, while others blame stringent regulation or the lack of oversight by Health Canada. The federal government mostly blames the provinces for their skewed procurement process, which favours sole suppliers. Many consider that the current shortages are the result of a "perfect storm" due to the convergence of multiple causes. But the real issue remains finding a weatherman capable of helping the Canadian healthcare system navigate the storm.

Drug supply is first and foremost organized through the market and relies on a precarious chain of suppliers of raw materials, manufacturers, wholesalers, distributors, hospital pharmacies and retail pharmacies. Any disruption in this delicate system can create significant shortages. The problem was well identified by the Canadian Pharmacists Association (2010):

> What is missing in the drug supply chain is any organization or party that holds accountability for the supply chain from a system-wide perspective. Neither government nor any third party has an oversight function for the drug distribution system, and therefore drug supply is dictated in large measure by the market. Due to the reluctance of individual manufacturers to share information on supply and manufacturing problems, it is difficult to predict when shortages will occur, for how long, and affecting which drugs.

While the Canadian supply chain for drug distribution mostly relies on a vague idea of "markets" (an odd term when applied to economic sectors organized with sole suppliers), we are now discovering the hard way that "markets" might not be doing a good enough job to maintain a stable supply of essential medicines in the Canadian healthcare system. Before recommending solutions on how to fix the system, however, it is important to understand why the system is broken.

Understanding the Global Generics Market

Drug shortages are not only a Canadian phenomenon; they are global "from Afghanistan to Zimbabwe" (Beerten and Bonheure 2011). Among the most acute shortages around the world, we find generic injectable chemotherapy agents, injectable anaesthetic agents, intravenous nutrition and electrolyte products, enzyme replacement products and radiopharmaceuticals (Gray and Manasse 2012). While shortages involve mainly generics, some shortages also occur with brand-name drugs. Injectable generics are most affected. In the United States, 74% of shortages in 2010 involved generic injectables (Koh 2011). For technical reasons, the production of injectables entails a much more complex manufacturing process than solid dosage forms, making compliance with quality-control regulations more difficult.

The global generic drug industry is in the midst of important transformations. The industry is both booming and going through a wave of mergers and acquisitions. According to a study by the IMS Institute for Healthcare Informatics (2011), global generic spending went from $124 billion in 2005 to $234 billion in 2010. The IMS Institute also estimates that generics will represent between $400 billion and $430 billion in 2015. If generics represented 20% of global drug spending in 2005, it will represent almost 40% in 2015. The boom is substantial, thanks in part to the major patent cliff faced by brand-name pharmaceuticals. These numbers contrast greatly with the expected stagnation in sales of brand-name products in developed markets in coming years. Little wonder that brand-name companies are restructuring by outsourcing production and research and development in "pharmerging countries,"[4] while simultaneously diversifying by acquiring generic companies in order to establish themselves in the growing generic markets (Tempest 2010). Dominant generic manufacturers are also merging or acquiring other companies in order to grow in this booming market. The four largest generics manufacturers worldwide – Teva, Mylan, Sandoz (owned by Novartis) and Watson – which together account for 40% of generic prescriptions worldwide, all used mergers and acquisitions to gain global market share (Harding 2010).

We are thus in a situation in which the global generic sector is producing at full capacity while undergoing major restructuring. Profitability is increasing in the sector, especially with the patent cliff that provides new possibilities in terms of generic production. Because generic manufacturers rationally focus on the most profitable products, they halt the production of cheaper generics that have low mark-ups. And because industrial mergers also tend to enlarge the size of assembly lines for reasons of economies of scale, halting a large assembly line can prove very disruptive in the whole supply chain. Standard economic theory considers that such shortages will be corrected by the law of supply and demand: the price of the scarce drug will increase, thus increasing profit, thus increasing production. The problem is that for the vast majority of generics, the price is fixed or established through long-term contracts, allowing for little short-term fluctuation. Moreover, drug purchasers like pharmacy benefits managers or hospitals' purchasing agencies are not price-takers: they normally buy such large quantities that they have the capacity to put downward pressure on drug prices.

Some media have emphasized shortages in raw materials, particularly of the active pharmaceutical ingredients (often produced in India or China). In the case of injectables, the lack of raw material does not seem to be a significant contributor to current shortages. In fact, in both 2010 and 2011, unavailable active pharmaceutical ingredients were cited by drug manufacturers as a cause in less than 10% of shortages (Koh 2011).

The North American Situation

The global market for generics might be booming and restructuring, but regional causes also explain why shortages have multiplied. The specific context of drug shortages in Canada must be understood by considering the American situation, because most Canadian generic manufacturers also produce for the US market. For example, many of the current shortages in Canada are a direct result of the heparin scandal of 2007–2008 in the United States.

Heparin is a generic blood-thinner. The company Baxter produced contaminated heparin in 2007–2008, apparently because the active pharmaceutical ingredient imported from China was contaminated. This led to as many as 81 deaths and hundreds of injuries linked to allergic reactions in the United States (Gardner 2008). The FDA took a lot of heat because of this episode. During the congressional investigation, it became clear that the FDA was underfunded and understaffed to achieve its task of enforcing quality-control regulations in the production of pharmaceuticals. Congress reacted by beefing up the FDA's funding, and the agency stepped up the number of its inspections. Under George W. Bush, each pharmaceutical plant was inspected on average 0.6 times a year; now, each plant is inspected almost once a year (Silverman 2011). It seems that the FDA's inspections are also more stringent, because the number of failed inspections increased from 20% in 2007 to 54% in 2010, and 80 drug makers failed more than half of the inspections (Silverman 2011).

When the FDA compels a drug maker to comply with quality-control regulations, it normally means that production must be halted or delayed in a context where shutting down large assembly lines might disrupt the whole supply chain. Lax enforcement of the rules brought

lax compliance and, following the heparin scandal, more stringent enforcement has created disruptions like the one involving Sandoz. For Paul Bisaro, CEO of the generic manufacturer Watson and head of the Generic Pharmaceutical Association in the United States, the solution to drug shortages is simple: put a halt to FDA inspections (Jack and Rappeport 2011)!

A more logical solution would be to maintain stable funding and staff for regulatory agencies (the FDA and Health Canada) in order to ensure that they can consistently enforce quality-control regulation. If there had not been lax enforcement in the first place, then regulatory standards would not have become a factor in the magnitude of drug shortages.

In Canada, some critics blame shortages on the hospitals' procurement methods, a tendering process in which the cheapest supplier wins the whole market. This system favours sole suppliers and makes finding an alternative supplier difficult in cases when production is halted. One solution could be to "favour competition" by purchasing drugs from multiple suppliers, but this path wouldn't be cheap. New Zealand went this route, and in 2009 the Pharmac annual review reported that dividing the tendering process in two increased prices on average by 17%. This is a significant price to pay for an "insurance premium." Generic manufacturers are certainly in favour of increasing prices, but this would be difficult to justify at a time when cost containment in healthcare services has become a priority. Furthermore, trying to create more competition in this sector in the context of global industrial mergers might prove futile, while impeding savings for Canadians.

Another solution would be to start stockpiling every critical drug in case something jeopardizes supply. We already stockpile antivirals, such as Tamiflu®, in case of a flu pandemic; why not do so with other drugs? Bear in mind that stockpiling products with an expiry date is not a rational solution. The example of Tamiflu® resulted in a waste of some $180 million for Canadians (and $1.5 billion for Americans), especially considering that the drug has not been shown to be more effective than Aspirin® (McKie 2011; Doshi and Jefferson 2012). There is certainly a case to be made for hospitals to stockpile reserves of critical drugs for an additional month, just in case, but a national stockpiling strategy at the federal level sounds like a blank cheque for massive waste.

Many are calling for the implementation of a national registry in which drug manufacturers would have to announce in advance any possibility of drug shortages. In the United States, the FDA implemented such a mandatory registry. In Canada, four non-mandatory registries exist.[5] Such a registry can certainly improve communication among manufacturers, regulatory agencies and healthcare organizations, but this approach comes with significant adverse effects. Announcing the possibility of a shortage normally triggers wholesalers and pharmacy chains to start massively buying and stockpiling drugs, accelerating the shortages. Since the implementation of the registry in the United States, "scalpers" have emerged: fake pharmacies set up expressly to buy large quantities of drugs in short supply in order to resell them with extremely high mark-ups. The mark-ups obtained by scalpers average around 650% (Cherici et al. 2011). For example, hospitals and healthcare providers faced a situation in which the cost of a generic beta-blocker for high blood pressure, labetalol, went from $25.90 a dose to $1,200 a dose.

There is certainly a good case for ensuring that hospitals and healthcare organizations stipulate, in the conditions of their tender, that the pharmaceutical supplier must bear the risks of shortages and pay any additional costs for the supply of alternative drugs. However, it could be counter-productive to introduce the technological tools that would allow malicious organizations to profiteer by inducing dearth.

Return of a Crown Corporation?

In her blog for *L'Actualité médicale*, a major medical newspaper in Quebec, Dr. Jana Havrankova (2012) suggests establishing a Crown corporation to produce generics in Quebec. In a recent meeting of the Canadian House of Commons Standing Committee on Health, devoted to tackling drug shortages, Dr. Joel Lexchin also suggested the implementation of a Crown corporation in Canada.[6]

The idea seems a bit far-fetched at first glance. Nevertheless, it might be an important strategic element to tackle drug shortages. Certainly, better communication between manufacturers and regulators is important; regulatory agencies must remain consistent in the way they enforce quality-control regulations; hospitals and healthcare organizations need to include more conditions in their tendering processes in order to shift the risks of shortages onto suppliers; and the federal government needs to identify critical drugs in order to develop emergency plans in case of disruption in supply. A Crown corporation that produces generics, however, could be a real strategic asset to consolidate the supply chain. Such a non-profit corporation could focus on the production of less profitable but clinically necessary drugs. It could ensure more beneficial tendering that favours sole suppliers and economies of scale. It would also allow greater price stability and discourage scalping. It might not be able to react immediately to a halt in production (for example, in the case of a fire at a major plant), but it would build up strategic capacity in the Canadian healthcare system to manage its supply chain in a more stable and efficient way.

Government-owned, public manufacturers of generic drugs are not unusual. In Sweden, Apoteket, the public network of pharmacies, is obliged by law to provide all drugs approved for marketing. To do so, Apoteket set up its own production facility to manufacture any unavailable drugs. In 2005, the company's production amounted to 1.2% of net sales in Sweden (Moïse and Docteur 2007). Thailand and Brazil use government-owned pharmaceutical companies as a "threat capacity" to reduce drug prices in a world dominated by sole suppliers.

Perhaps Canada has also arrived at a point where having a Crown corporation in the pharmaceutical sector might be an important element in obtaining better outcomes than "market forces" have provided. Some critics might consider such a proposal politically unfeasible. However, Joel Lexchin reminded the Health Committee that a Crown corporation – the Connaught Laboratories[7] – existed for the production of vaccines in the 1970s and 1980s. In Quebec, two political parties with elected MPs are already demanding the establishment of "Pharma-Québec," a bulk-purchasing agency coupled with a public generic manufacturer. In the end, the idea might not be so far-fetched.

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NOTES

[1] See the FDA warning letters at www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm281843.htm. (Retrieved April 18, 2012.)

[2] See their joint press release dated March 12, 2012: www.newswire.ca/en/story/936157/canada-s-pharmaceutical-industry-comes-together-to-address-drug-shortages. (Retrieved April 18, 2012.)

[3] There are no clear data about the evolution of drug shortages in recent years. However, 97% of pharmacists surveyed by the Canadian Pharmacists Association (2010) considered that drug shortages increased between 2009 and 2010. In a similar report produced in 2004, the CPA stated that actual shortages are "more widespread and prolonged."

[4] "Pharmerging countries" are emerging markets including China, Brazil, Russia, India, Mexico, Turkey, South Korea, Venezuela, Poland, Argentina, Vietnam, South Africa, Thailand, Indonesia, Egypt, Pakistan and Ukraine.

[5] The four registries identified by Rx&D and the Canadian Generic Pharmaceutical Association are Vendredi PM (www.vendredipm.ca); University of Saskatchewan Drug Information Services (www.druginfo.usask.ca/healthcare_professional/canadian_drug_shortages.php); Canadian Drug Shortage Database (www.canadapharma.org/shortage/index.asp?l=en); and Canadian Generic Pharmaceutical Association (www.canadiangenerics.ca/en/resources/shortages.asp).

[6] Minutes and webcast are available at www.parl.gc.ca/HousePublications/Publication.aspx?DocId=5496428&Language=E&Mode=1&Parl=41&Ses=1. (Retrieved April 18, 2012.)

[7] For the history of the nationalization and privatization of Connaught, see Paterson 1996.

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