THE MULTI-STAKEHOLDER STEERING COMMITTEE ON DRUG SHORTAGES IN CANADA

Preventing Drug Shortages:

Identifying Risks and Strategies to Address Manufacturing-Related Drug Shortages in Canada

Revised in 2017

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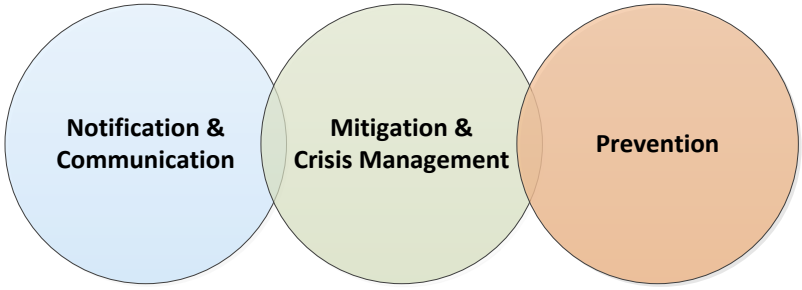
1. BACKGROUND

1.1 Multi-Stakeholder Steering Committee on Drug Shortages

The Multi-Stakeholder Steering Committee on Drug Shortages (MSSC) was established in 2012. It includes representatives of industry associations; federal, provincial and territorial governments; and health professional associations, coming together to address drug shortages in a collaborative and coordinated manner. The MSSC recognizes that a consistent and reliable drug supply is important for the health and safety of Canadians, but that drug shortages do occur and are a complex, global problem involving all stakeholders across the drug supply chain.

The Committee's workplan includes three integrated pillars:



To date, collaborative efforts of the MSSC have resulted in progress on how to address drug shortages through the first two pillars, including industry's commitment to the public notification of shortages and discontinuations, first on the industry-run www.drugshortages.ca and then, following the introduction of the Regulations on Mandatory Drug Shortage and Discontinuation Reporting in 2017, on www.drugshortagescanada.ca; improved coordinated and collaborative action on recent drug shortages; and the development of the following suite of publications:

- *MSSC Multi-Stakeholder Toolkit*, which describes the Canadian drug supply chain, clarifies roles and responsibilities of key players, and identifies the tools and strategies available to address drug shortages at specific stages of the supply chain;
- *MSSC Protocol for the Notification and Communication of Drug Shortage*, which sets out clear expectations for the notification and communication of information in anticipation of or response to a drug shortage; and
- *Guidance Document to Mitigate Drug Shortages through Contracting and Procurement*, which outlines best practice contracting guidelines, procurement strategies, and tools to address common drug supply chain shortage vulnerabilities.

In 2013, for the next phase of collaborative efforts, MSSC committee members shifted focus to drug shortage cause and prevention. Consistent with this direction, a Cause and Prevention Working Group was formed, including key members of the MSSC as well as industry manufacturing representatives. Given that globally, the most commonly cited source of drug shortages are manufacturing issues, this working group has sought to identify, analyze, and propose strategies to reduce and prevent the manufacturing-related causes of drug shortages in Canada. These manufacturing-related causes include, but are not limited to, production or market issues, regulatory compliance issues, unexpected surges in demand, and difficulties obtaining raw supplies.

While it is acknowledged that preventing drug shortages is a multi-stakeholder responsibility, this report aims to address an important first piece of the prevention puzzle.

1.2 Purpose and Objectives of Report

The purpose of the *Preventing Drug Shortages: Identifying Risks and Strategies to Address Manufacturing-Related Drug Shortages in Canada Report* is to identify, analyze, and propose strategies to mitigate and prevent the manufacturing-related causes of drug shortages in Canada.

It is the MSSC's expectation that industry stakeholders, particularly drug manufacturers:
1. Identify gaps between existing manufacturing structures and processes against best practices and recommendations delineated in this report.
2. Confirm their commitment to consider how recommendations could be applied to the existing manufacturing structure of the organization.
3. Where possible, implement recommendations into the current business architecture, with the aim of preventing future drug shortages.

1.3 Methodology

The MSSC Working Group surveyed Canadian pharmaceutical (brand and generic) and biologic drug manufacturers to identify and describe risks within the drug manufacturing supply chain that have the potential to lead to supply disruptions or actual drug shortages. Manufacturers were also asked to propose prevention strategies and best practices to mitigate these risks, and thereby reduce the chances of manufacturing-related drug shortages.

The MSSC compiled this input, examined and reviewed the risks and prevention strategies, and formulated key recommendations for implementation. This report presents the results of these efforts, a valuable gathering of information and recommendations specific to drug manufacturers and the role they can play in preventing drug shortages. For a complete list of contributors, see Appendix B.

1.4 Scope of the Report

As denoted in the figure below, the manufacturing process is only part of the greater life cycle of a drug. Prior to marketing, the drug must be researched, undergo clinical trials, be reviewed and granted market authorization by Health Canada under the federal *Food and Drugs Act*. Additionally, after the drug is manufactured for market, it will have to maneuver through the remainder of the supply chain until it reaches its market destination (e.g., hospital or pharmacy). This Report only considers the potential risks for drug shortage *within the drug manufacturing process* as described below and in Figure 1.

→ The **primary phase** of the drug manufacturing process involves identifying and sourcing ingredients, including active pharmaceutical ingredients (API) and excipients in appropriate amounts per dose. Depending on the choice of pharmaceutical forms (tablet, ointment, solution for injection, etc.), appropriate manufacturing processes and controls are selected to meet the expected quality attributes.

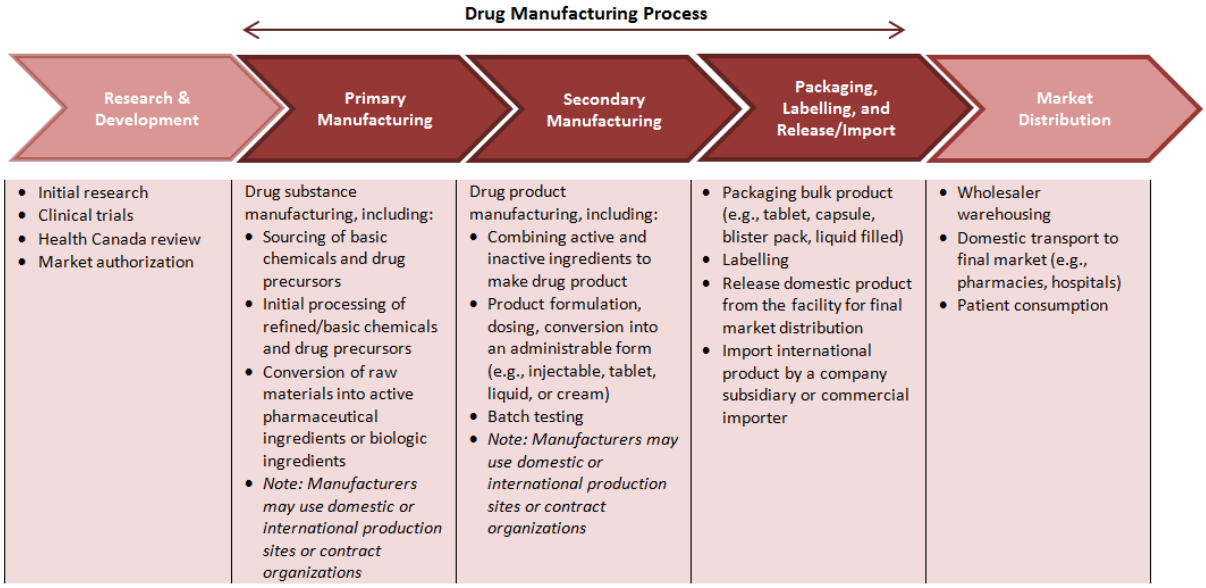
→ Next, based on the product development research completed above, the **secondary phase** combines the API with inactive, non-medicinal ingredients as per the chosen manufacturing

process. This could be a relatively simple process of dissolving the API in an aqueous medium like ibuprofen syrup for children or a complex process to manufacture sterile implants for contraception that would release precise amount of drug over several months. In between, are the more common forms of drug products marketed in Canada, such as tablets or injectables. For tablets, the chemical components are combined in a series of steps to complete the product formulation, including mixing active and inactive ingredients, drying, crushing and sieving, before compressing into tablets. For injectables, the API and other required excipients could be dissolved in water for injection, filtered, packaged in sterile vials or ampoules and finally sterilised. Some injections could be sterile suspensions or freeze-dried powders. Quality control is closely monitored at various stages during manufacturing to ensure the finished product meets precise specifications; this might include inspecting for assay, purity, particulate contamination and/or sterility.

→ Finally, **the packaging, labelling, and release phase** involves preparing the drug product for distribution, sale and use.

All manufacturing phases, as well as product manufactured for clinical testing and distribution, are subject to Good Manufacturing Practices (GMP) requirements under the *Food and Drugs Act* and its Regulations.

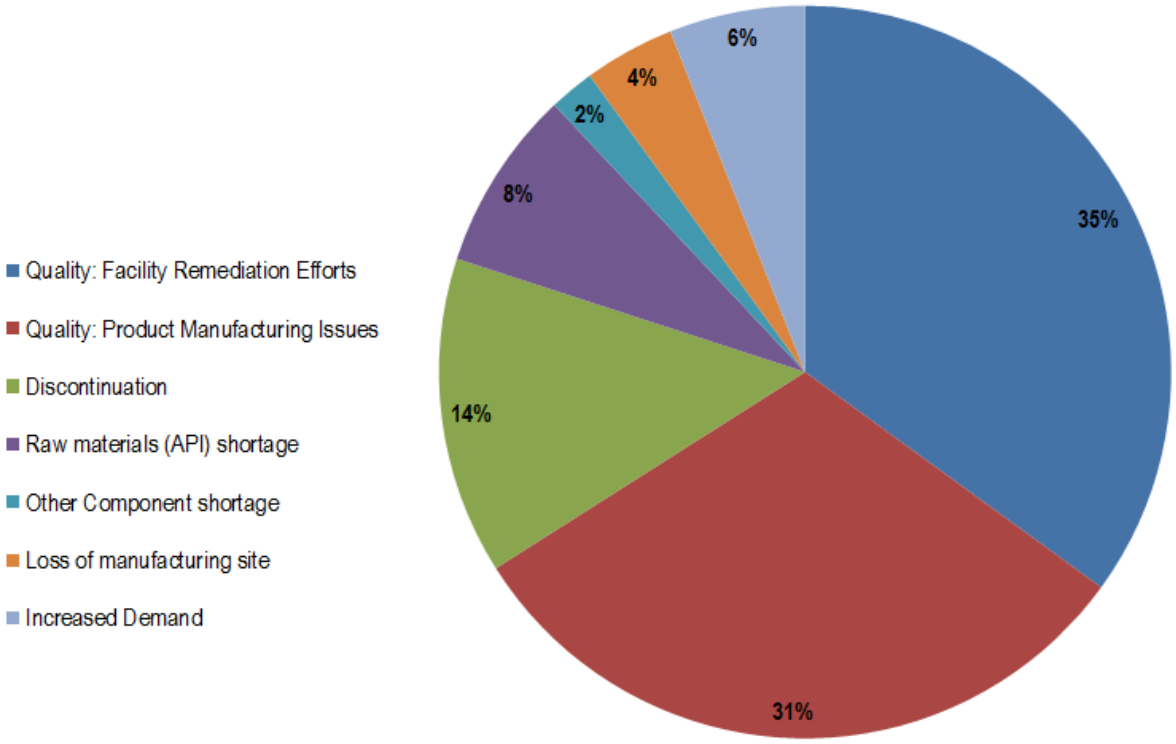
Figure 1 – Drug Manufacturing Process



While recognizing that there are risks for supply disruption during the market distribution phase, statistics[1] have shown that the majority of drug shortages arise as a result of manufacturing and quality issues during production (see figure 2 below).

[1] There are currently no comprehensive, publicly available Canadian data on which drugs are in short supply and why, and the information available from individual databases is highly variable. It is for this reason that US FDA data is frequently used as a proxy to represent the Canadian experience.

Figure 2 – Causes of Drug Shortages



Source: US Food and Drug Administration
http://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM372566.pdf

2. OVERVIEW OF CANADIAN DRUG MANUFACTURING INDUSTRY

2.1 Global Context

As a whole the global pharmaceutical industry develops, produces and markets drugs for use as medications to cure, manage, and protect us from diseases and infection. The industry is made up of a small number of large multi-national corporations and a larger number of smaller drug producers (i.e. the 10 largest drug companies share over one-third of the market).

There are several sub-sectors of the pharmaceutical industry, including:

Brand-name pharmaceuticals companies: Focused on research and development (R&D), these large multi-national corporations discover, develop, and seek regulatory approval for new chemical compounds that become brand-name drugs and medications (i.e., drugs with patent protection). Patent protection enables the manufacturer to recover the costs of R&D through higher profit margins for the branded drug.

Generic drug companies: When a drug goes "off patent," other drug manufacturers are able to produce and market comparable versions of the drug, referred to as generic drugs. Generic drugs are bioequivalent to (i.e. their active ingredients are chemically identical), and are typically sold at a lower price than the brand name version.

Biopharmaceutical small and medium sized enterprises (SMEs): Biologic drugs include a wide range of products such as vaccines, blood, gene therapy, and tissues. Unlike traditional chemically composed drugs, biologics are manufactured using living systems such as a human, animal, or microorganism.

Contract manufacturing organizations (CMO): Manufacturing organizations which are contracted by drug corporations to undertake some part(s) of product conversion activities (e.g., formulation, clinical trials, manufacturing, fill and finish, chemical synthesis, analytical testing and other laboratory services, and packaging and labeling).

Over the past several decades, growth in the global pharmaceutical industry was driven by patented "blockbuster drugs" – extremely popular drugs that generate annual sales of at least $1 billion for creators. The cost of bringing a new drug to market is very high (estimates average US$800 million), and is known to extend over a period ranging from 8 to 15 years. Patent protection for widely prescribed medicines enables cost recovery for the substantial investments required to get them there.

Since the 1990's, R&D has not generated the same volume of blockbuster products and therefore drug manufacturers are responding by focusing research on specialty medicines, such as oncologics, immunostimulants, and antivirals. Where blockbuster drugs were easily targeted to a large population, new R&D is looking to create a multitude of drugs targeted to a smaller population and differentiable for patenting purposes. The industry is also seeing an increase in the number of mergers and acquisitions, as larger corporations look to acquire smaller research-focused businesses that are showing promising R&D outcomes.

In order to reduce fixed costs and overcapacity, brand-name and generic corporations have significantly increased the outsourcing (domestic and international) of several manufacturing

stages including sourcing of APIs, product manufacturing and packaging through CMOs, as well as R&D activities.

2.2 Canadian Context

Canada plays an important role in the global pharmaceutical industry. Canada's pharmaceutical sector is composed of companies developing and manufacturing innovative medicines and generic pharmaceuticals, as well as over the counter drug products. The sector is made up of a number of sub-sectors that service different market segments, including brand-name pharmaceuticals companies, generic drug firms, biopharmaceutical SMEs and CMOs.

Pharmaceutical sales in Canada have a 2.5 percent share of the global market, making Canada the 9th largest world market. From 2001 to 2013, pharmaceutical exports and imports between Canada and the rest of the world increased by 155 and 96 percent, respectively. More than half of Canadian production is exported (primarily to the United States) and a significant portion (62.3%) of the Canadian market is supplied by foreign imports.[2]

Market segments driving the Canadian pharmaceutical market reflect considerable changes and contrasts in growth. In the past ten years, the Canadian market has seen dramatic growth in generics as a result of patent expiries and policies by payers targeting generic utilization. As of December 2015, generics account for 68.6% of total prescriptions in Canada.[3]

Canada's pharmaceutical industry consists of a mix of multi-national and local companies. Most major brand and generic pharmaceutical companies are foreign multinationals with subsidiaries in Canada. Generally, Canadian-headquartered companies in the industry are relatively smaller and serve niche specialty segments of the industry. These smaller companies are more numerous than multi-national companies, but multi-national companies are dominant in terms of their size and sales in the Canadian market. Biopharmaceutical SMEs in Canada are small and generally focused on early stage R&D with few marketed products. CMOs have also become a major player in the industry, with a mix of local smaller Canadian-headquartered companies and larger foreign companies. These CMOs provide a wide array of contract services in the product lifecycle, from R&D and manufacturing to sales and administration.

[2] Industry Canada. **Pharmaceutical industry profile**. *http://www.ic.gc.ca/eic/site/lsg-pdsv.nsf/eng/h_hn01703.html*
[3] Data from IMS Health Canada Inc.

3. UNDERLYING CAUSES OF MANUFACTURING-RELATED DRUG SHORTAGES

3.1 Context

While not every drug supply disruption will turn into a shortage, nearly all shortages are preceded by a disruption in supply. As noted in the previous section, the root cause of many supply disruptions can be traced back to aspects of the manufacturing process. These disruptions can be attributed to a variety of risk factors, including drug quality issues (GMP or otherwise) that result in delays, recalls, regulatory compliance enforcement actions, drug discontinuations, and unavailability of raw materials, including APIs.

Understanding the manufacturing-related risk factors that are more likely to lead to a shortage is an essential first step to the identification of corresponding mitigation and prevention measures. This section outlines the key risks in the manufacturing process that could result in a drug shortage.

3.2 Manufacturing-Related Risks

3.2.1 Primary and Secondary Manufacturing

Raw material supplier delays

Disruptions in the supply of raw materials, including APIs, are a frequently cited source of drug shortages. Drug manufacturers are increasingly importing raw materials from other countries, making them reliant on a global supply chain and susceptible to different risks than the domestic market (e.g., transportation, customs clearance, weather, and quality documentation).

Raw material supply disruptions can result from a number of factors, including a manufacturer ceasing operation, delivery delays, political upheaval, natural disasters, degradation or contamination during transport, animal diseases, or decreased yields of plants used to source raw materials.

Furthermore, international regulatory bodies continue to expand their scope of oversight, including GMP requirements for API suppliers. When an API supplier fails to comply with GMP requirements of a regulatory body, a supply disruption, affecting many jurisdictions, may result from the requirement to immediately implement remediation efforts.

Disruptions in raw materials can be particularly problematic when multiple manufacturers are producing a drug product from which there is only one source of raw materials. As a result, any interruption in the supply of that raw material will affect all of the manufacturers using it in their finished drug product.

Similarly, historical competitive proposal practices have often decreased manufacturers' ability to respond rapidly to supplier disruptions when they occur. For example, single-award contracts make it difficult to source alternative raw materials when the primary supplier cannot meet agreed upon quantities. Also, competitive proposal practices favouring price with a less consideration of supplier historical quality and reliability could encourage a continued downward spiral in supply chain performance, thereby increasing potential for more shortages.

Raw material quality assurance (QA) testing failures

Because the quality of the ingredients has a direct effect on the safety and efficacy of that drug, regulations under Canada's *Food and Drugs Act* require that manufacturers open and sample each container of raw materials, including excipients, APIs and bulk process intermediates. Ingredients are tested for, among other things, residual solvents/impurities, extractables, degradation, and trace materials.

Detecting issues at this stage with APIs or excipients, such as cross-contamination with other APIs, altered crystal forms or particle sizes, or changes in impurity profile, can avoid the release of unsafe product into the market. However, batch or internal audit failures can also result in delays in production that could lead to a drug shortage.

Further, when raw material QA issues are coupled with subsequent supplier delays for replacement product (referenced above), the interruption is compounded for the manufacturer.

Importing issues

Most drug manufacturers import some or all production ingredients from abroad (e.g., many APIs are imported from India and other parts of Asia). This step introduces another threat in the supply chain as there are a number of risks associated with the transfer and import of these products. To ensure the quality of products and prevent the entry of illegal or counterfeit products into the supply system, Canadian *Food and Drug Regulations* (like other international laws) require the importer conform to prescribed standards, processes and documentation.

In some cases, when these requirements are not met, imported products can be seized by regulators/inspectors or destroyed in transit. For example, if a Canadian importer cannot properly attest GMP compliance status of the foreign buildings where APIs originated, the product will be refused entry. Alternatively, if the pharmaceutical ingredient was not properly protected against temperature excursions or weather conditions, entire imported shipments could be destroyed, leaving the manufacturer to find an alternate source of the ingredient or delay their production schedule until the resolution of the import issue.

Quality failures involving manufacturing process

All drug manufacturing in Canada must meet applicable GMPs as set out in the *Food and Drugs Act* and its *Regulations*. GMPs ensure that drugs are consistently produced and controlled in such a way to meet the quality standards appropriate to their intended use. Quality failures can result from issues in production quality, facilities quality or process quality. If a pharmaceutical does not meet established quality standards, the possible consequences may include toxic and adverse reactions or lack of therapeutic effect, which may lead to prolonged illness or death.

Pharmaceutical quality can be assessed by the product's compliance with specifications relating to identity, purity, strength, potency, uniformity of the dosage form, bioavailability, and stability. Some examples of causes of manufacturing quality issues include:

- → Sterility (e.g., bacterial and fungal contamination)
- → Particulates (e.g., glass, metal or fiber in vials)
- → Crystallization (e.g., drug may form crystals)
- → Precipitation (e.g., reaction between the drug and container or diluent)
- → Impurities (e.g., can be toxic, such as heavy metals)
- → Degradants (e.g., lead to less effective drug product)

Once a quality failure is detected, the manufacturing facility may be forced to shut down production in order to remediate the cause of the problem. Depending on the seriousness of the problem and the required steps to address it (e.g., decontaminating equipment to full facility upgrades), this could result in temporary supply constraints or prolonged shortages.

In many cases, facility equipment is used to manufacture more than one product, therefore in the event of facility or equipment shut down, a number of product lines may be at risk for supply disruption.

Lack of alternate manufacturing options

Some drug products such as vaccines, sterile injectables and biologics, have highly specialized and complex production processes that make it difficult or impossible to quickly find alternate manufacturing options in the event of a facility shutdown or loss of manufacturing capacity.

For example, biologic production uses specialized manufacturing processes that do not resemble the facilities, machinery, or equipment used to produce many chemical drugs, and construction of new facilities is disproportionately expensive and time consuming.

Similarly, it is often challenging to scale-up production of these products to meet a sudden increase in market demand.

3.2.2 Packaging, Labelling, and Release/Importation

Packaging errors and packaging component shortages

Pharmaceutical packaging is the final step in end-product preparation. Effective and accurate packaging is vital to the safety and quality of the product. To illustrate, proper packaging will effectively protect the product from the environment (humidity, light, oxygen, bacteria, etc.); provide critical information related to expiration, safe preparation, safe use, storage, and disposal; enable accurate dosing compliance; and ensure trace-back capability and anti-counterfeit measures.

Human or technological errors in the production cycle can result in mislabelled products such as text errors and mixing-up of packaging components. At the outset labelling errors may not appear to be serious; however, sound-alike and look-alike drug names and packaging can lead pharmacists and other health professionals to perform unintended interchanges of drugs that can result in patient injury or death. When these types of mistakes are made on a large scale, impacts can be substantial, including recall, product write-off, repacking, and a partial or full market re-supply.

Similarly, long lead times resulting from shortages of packaging components (e.g., labels, blister packs, gelatin capsules, aluminum tubes) can result in lengthy lags in production.

Transport issues

Pharmaceutical products are vulnerable to a wide range of hazards while in transport, either domestically or imported. Environmental controls play a key role in maintaining drug safety, quality and efficacy. For example, temperature excursions outside the labelled storage conditions could affect the efficacy of the active ingredients, rendering the batch unusable and potentially dangerous. As distribution logistics become more complex and multi-staged, there are many more touch points along the way where product is susceptible to adverse environmental conditions.

Additionally, the mode of transport introduces different risks with respect to timing, check-points, and environmental exposure.

3.2.3 Universal Risks: risks that cut across all phases

Unforecasted increases in product demand

Unexpected demand for a drug can lead to a shortage when domestic and international supply cannot keep pace. Increases in market demand can result from a new indication for an existing drug, changes to clinical guidelines, or disease outbreaks. These changes can be further exacerbated when the manufacturing process for a drug is lengthy or the raw materials required to produce it are limited.

Increased demand can also occur when a supplier of a multi-sourced drug (i.e., more than one manufacturer) experiences a supply disruption or makes a business decision to discontinue the drug. This reduction in supply capacity may drive up demand and deplete the product inventories of the remaining suppliers.

Business decisions

Supply disruptions can also occur due to a business decision made by a manufacturer. For example, a manufacturer may permanently discontinue or temporarily reduce production of certain drugs as they shift production or reallocate resources to another product.

Factors that can lead to the decision to permanently or temporarily reduce the production of a drug could include: diminishing demand; insufficient profits; introduction of generic products; costs to adhere to regulatory requirements; or expense to remedy manufacturing problems. Likewise, consolidations and mergers may result in supply disruptions based on a decision to narrow the focus of the product line, discontinue products or to shift manufacturing to another facility.

Disruptions due to regulatory actions

Supply interruptions, as a result of regulatory action due to GMP non-compliance, can occur at any point in the manufacturing process when an existing regulation, local or international, is not adhered to. Manufacturer failure to comply with regulatory standards can result in a range of regulatory actions taken by Health Canada, or other international regulatory agencies, including warning letters, seizure of a product, recalls, and fines.

If, for example, the US FDA issues a Warning Letter to a manufacturer in China, who also supplies a major producer in Canada, supply of that product (e.g., API) could become in shortage while the Chinese company takes steps to correct the GMP violations.

Similarly, actions taken by Canadian compliance and enforcement authorities will have effects on the domestic drug supply. To illustrate, commercially imported drugs (either finished product or ingredients) can be seized and refused entry if the inspector has reasonable grounds to believe any provision of the *Food and Drugs Act* or its *Regulations* have been contravened (e.g., improperly labelled, suspected counterfeit, etc.).

Drug companies in violation of regulations may have to halt or reduce production in order to address the non-compliance issue. Regulatory actions have become more common for

manufacturers located in countries that have less stringently enforced safety and regulatory standards (currently approximately 80% of domestic APIs are sourced overseas).

Lack of coordinated communication

While supply disruptions in the manufacturing process are not always avoidable, the steps taken after the initial detection of a problem are entirely within the control of the manufacturer. However, when the communication infrastructure within an organization is not structured, dynamic and responsive, information lags can become commonplace. For example, vague procedures for when to report potential issues to the head office, a lack of protocol for routinely communicating quality metrics, or slow dissemination of shifts in market conditions can all contribute to the likelihood of a drug shortage.

4. DRUG SHORTAGES PREVENTION

4.1 Context

Drug shortages have been a growing concern for manufacturers, the healthcare industry and patients over the past decade. It is a complex issue that has required a multi-stakeholder response, including manufacturers, governments and healthcare providers. Manufacturers, however, have a particularly critical role in preventing these occurrences as they have the greatest amount of influence over the volume of product in the supply chain. As a result, manufacturers must respond with strategies that address the above risks within the manufacturing process in order to reduce the frequency and scope of supply disruptions.

The following section describes the strategies that, when implemented, have the potential to target manufacturing-related risks and reduce the incidence and limit the fallout of drug shortages in the Canadian market.

4.2 Industry Prevention Strategies

4.2.1 Supply Chain Management

The pharmaceutical supply chain is a complex network that is organized to take a product from its production stages at primary and secondary sites and distribute it to final markets. A typical supply chain will involve numerous contracts and agreements with external organizations including secondary manufacturers, packagers, importers, warehouses, local and regional distributors and retailers.

Particularly for larger multi-national producers, each phase of the manufacturing process will likely involve the product and its components moving between different processing sites. Because even minor disturbances in the supply chain could lead to significant disruptions in the supply, manufacturers must increasingly invest targeted resources into supply chain management and achieving a corporate quality culture. Key supply chain management strategies are described below.

Contracting due diligence

There are inherent risks associated with entering into a supplier or third party processing contract such as poor GMP compliance, financial uncertainty, and weak organizational/facility capacity. As a result, manufacturers should allocate a greater amount of attention and resources to the selection process, which includes:

- Confirming valid Drug Establishment Licence, or equivalent certifications from applicable agencies if the organization is outside Canada;
- Demonstrating financial stability to meet short term and long term obligations;
- Requiring verifiable references and reviewing the detailed history of experience with the particular manufacturing process;
- Confirming applicable product liability insurance;
- Requiring copies of inspection reports by Health Canada or equivalent international regulatory bodies in the country of origin;
- Calling for a list of alternative suppliers to avoid shortages in the event of a business interruption;

- Evaluating contractor's understanding of Health Canada regulatory requirements, basic quality control measures, and compliance; particularly for international facilities;
- Assessing manufacturing, distribution and storage standard operating polices;
- Inquiring about resource capacity to ascertain the contractor's ability to fulfill performance expectations;
- Ensuring the right of the manufacturer to perform unlimited on-site audits and inspections at subcontracted facilities; and
- Having in place a "back-up" plan or avoiding sole sourcing practices.

Recommendation 1
Include a contractual obligation for suppliers to maintain a list of alternative vendors in the event of a business interruption.

Recommendation 2
Perform more frequent and unannounced on-site audits and inspections at sub-contracted facilities.

Robust quality agreements

To ensure GMPs are maintained whilst relying on third party suppliers and processors, detailed quality agreements should become a standard component of these contracts. For example, these agreements could include:

- organizational capacity requirements;
- strict performance indicators reported on a consistent basis;
- regular meetings with subcontractor;
- requirement for subcontractor to conduct regular inspections of incoming raw materials and random batch testing of finished product;
- ongoing data reporting;
- consequences for non-compliance; and/or
- ongoing compliance monitoring and reporting of any actions taken by any regulatory authority.

Recommendation 3
Define comprehensive quality requirements in sub-contracts that, at a minimum, meet GMP as stipulated in the federal *Food and Drug Regulations*.

Effective communication

Disruptions can occur at any point in the supply chain, and sluggish communication and system alert speeds can significantly increase the chance that even a minor disruption in the manufacturing process results in a drug shortage in the market. It is also critical that problem escalation protocols exist within the organization to protect from poor communication between departments, sites, or subsidiaries when quality problems arise. Manufacturers should incorporate a suite of

communication tools to ensure information moves swiftly though the supply chain to mitigate the impacts of disturbances in the system.

For example, a growing number of businesses are integrating social media tools such as real-time conversations, blogs, wikis, eAlerts, and document sharing applications, into traditional communication structures like operational and planning meetings and dedicated working groups. These real-time information systems enable internal and external supply chain agents to receive near instant feedback, input, and solutions to operational problems, even when functional groups are geographically distant.

Recommendation 4

Integrate effective internal and external real-time communication systems that combine contemporary tools, such as social media and document sharing applications, with more traditional communication structures and communication protocols.

Supply chain analytics

Supply chain analytics are used to measure, monitor, and improve individual business processes as well as the overall performance of the pharmaceutical supply chain. For example, manufacturers collect and analyse data from within the supply chain to calculate the most favourable facility design, apply economic principles to forecast inventory requirements, and use formulas to define optimal safety stocks. Key performance indicators are evaluated at crucial phases of the manufacturing process such as production efficiency, batch output quality, as well as transportation and warehousing results. Effective analysis of available leading (predictive) and lagging (past performance) indicators helps manufacturers to better prevent future drug shortages of their products by performing root cause analyses, and sanctioning corrective and preventive actions before issues become severe.

Pharmaceutical corporations are increasingly realizing the benefits of "big data" – which reflects the ability for businesses with large, and in many cases multi-national, supply chains to capture and manipulate considerably larger datasets (significantly more volume, variety, and with greater velocity). "Big data" analytics can help manufacturers improve their ability to react more quickly to inefficiencies in the supply chain; gain insights about the future, rather than only reporting on what happened in the past; and achieve a cross-functional view of the supply chain to help optimize overall supply chain performance.

Recommendation 5

Employ supply chain analytics to detect issues in the system before they become a supply problem, by identifying the most effective key performance indicators, and developing the capacity and skills to work with and benefit from "big data".

Continuous improvements

Manufacturers who most effectively utilize the above noted supply chain management strategies are applying what they learn to make continuous improvements in their systems, such as: recognizing the need for investments in capacity and skills to manage supply chain activities, severing or renegotiating contracts with third party processors, making additional investments in resources, sites and equipment, as well as making enhancements to the manufacturing process.

Improvements in product quality (for in house and third party product) should also be steadfastly pursued using stringent quality control systems that address the root cause of the quality issue.

Comprehensive examination of drug shortages, supply disruptions, and near misses should also inform organizational improvements by assessing root causes, supply chain implications, and healthcare system consequences.

Recommendation 6
Make continuous investments in capacity and skills to ensure quality processes are maintained and GMP are met. Investments should not only be made within the organization, but for sub-contractors as well, as required.

Some tools that should be employed to improve the quality of end products include well designed key performance indicators, quality-by-design manufacturing (emphasises risk-management in the design, development and manufacturing), frequent and ongoing quality evaluations, and immediate corrective and preventative actions once a quality issue is detected. Key organizational practices might include:

- use of early warning signals such as complaint trends;
- frequency of internal audit inspections;
- frequency of equipment inspection/maintenance; and
- reportable quality metrics like pass/fail rates of key processes such as batch failure, sterility and stability.

Fundamental improvements to production quality and supply chain integrity will likely lead to fewer disruptions in the manufacturing process, thus reducing the chances for major drug shortages in the market.

Recommendation 7
Continually evaluate and adapt advanced quality assurance practices and systems, such as quality-by-design and quality metrics, to reduce the frequency and extent of supply disruptions.

4.2.2 Inventory and Product Specific Risk Management

Manufacturers are faced with finding a delicate balance, where enough inventory should be available to fully meet demand, but not enough that batches expire before going to market. To avoid drug shortages, supply chains and inventory management systems need to be nimble enough to adjust to fluctuating market demand, without substantial waste. Manufacturers must also be aware of the status and location of their product throughout the drug manufacturing process, until it is delivered to the client. Loss of inventory due to preventable errors in storage and distribution could lead to an unnecessary shortage of supply in the market.

Forecasting

Within the pharmaceutical industry, demand volatility is one of the greatest business risks and operational challenges. Predicting the demand for drug products, and in turn, the required

production volume in a given timeframe, is a highly complex process that involves estimating the potential number of patients (epidemiology and disease growth rate), the number of patients currently on the drug, dosing rates, as well as formulary and regulatory decisions.

Collaborative demand forecasting, a strategy used by some consumer goods industries, could potentially improve pharmaceutical industry forecasting outcomes. It typically sees manufacturers, distributors, and retailers sharing data for sales and operations planning in order to reduce overproduction and avoid demand shortages. Novel approaches like this, and other improvements to forecasting methodologies will help diminish the chance of an inventory related shortage, while at the same time; reduce wastage and expiry of valuable product in the supply chain.

Recommendation 8
Improve demand and supply forecasting capability by effectively utilizing market awareness and statistics, as well as incorporating innovative methodologies such as collaborative demand forecasting.

Inventory tracking

In the event of a potential supply disruption, whether faced by the manufacturer or a competitor, it is essential that inventory can be accurately accounted for at any phase of the manufacturing process. Having this real-time information at hand allows the manufacturer to:

- immediately quantify the supply disparity resulting from the disruption;
- expedite the distribution of otherwise idle inventory within the supply chain;
- execute product-specific allocation contingencies; and
- determine needed ramp-up of production where possible (especially in cases where disruption originates from a competitor).

To achieve a precise end-to-end picture of available stock in the supply chain, manufacturers must effectively connect with processors, importers, warehousing, distributors, and retailers – echoing the supply chain management strategies described above.

Recommendation 9
Upgrade inventory tracking systems to enable real-time communication with the supply chain.

Allocation systems

Recognizing that certain drugs, particularly those considered "medically necessary"[4] require special consideration during a supply disruption, manufacturers have been establishing product-specific allocation programs based on market utilization. Manufacturers should have processes in place to handle low stock situations and potential shortages, applicable locally and throughout global operations. These processes could include centralizing distribution of a product to control how much and to whom product is released; prioritizing allocation based on high need/urgent circumstances; or ensuring that retailers order appropriately (i.e. no large orders during a shortage

[4] Canada has not established a consensus on the term. However, according to the US FDA, "medically necessary" drugs are those "*used to prevent or treat a serious or life-threatening disease or medical condition, for which there is no other available source with sufficient supply of that drug or alternative drug available.*"

situation). Moreover, for some products with limited or no alternative suppliers (i.e. high risk), manufacturers should build into production forecasts the need for safety stock in the event of a disruption or shortage.

Recommendation 10
Incorporate product-specific inventory allocation systems that prioritize high-risk products by ensuring safety stocks and identifying high-priority retailers in the event of a shortage.

4.2.3 Contingency Planning

Contingency planning is an important element of risk management for most businesses. However, for manufacturers of drugs, particularly those that are considered medically necessary, risk management strategies must include reducing the chance that patients suffer health consequences as a result of planned business decisions or unplanned supply disruptions. Contingency planning for these events can ease the gap between a drug shortage and resupply.

Alternate sub-contractors

Greater diversity in the drug supply chain in the form of approved alternative or backup suppliers, sub-contractors (e.g., laboratories, packaging, release testing facilities, etc.) and production sites can reduce the overall effects of disturbances in the primary supply chain. Contracting with, or at the very least, getting regulatory approval for alternative sub-contractors will enable producers to be more nimble and responsive in the face of disruptions within their manufacturing supply chains.

While it may not be a realistic business strategy for producers to have alternate sub-contractors ready for *all* steps in the production cycle, companies should work hard to identify back-up contingencies for any and all high risk areas, particularly for high risk products that have potential for more negative impacts on the Canadian market (e.g., treats or prevents life-threatening conditions or has limited alternative suppliers).

Recommendation 11
Identify or contract with approved alternative sub-contractors at all stages of the manufacturing supply chain, particularly for high-risk products.

Market knowledge

Most commercially producing drug companies hold a certain level of competitive intelligence as part of standard business performance strategies. However, this type of knowledge can also be used to mitigate a supply disruption, especially for drugs considered medically necessary. In the event of a supply disruption or shortage, if a manufacturer has and willingly shares their market knowledge, it can help stakeholders expedite a resolution by providing viable alternate domestic and global sourcing options. For those products without therapeutic alternatives, having firm and trustworthy alternate sub-contractors (as described above) should be considered a critical part of risk management.

Recommendation 12
Improve strategic market awareness to help predict demand changes and mitigate supply disruptions.

4.2.4 External Communication and Collaboration

As detailed in the MSSC *Toolkit* and *Communication Protocol*, a critical component of mitigating the effects of any supply disruption or drug shortage is through ongoing and transparent communication between drug supply stakeholders. As the player with the most complete information regarding the cause of the shortage, resupply dates, and market information, manufacturers must take more of a leadership role to ensure stakeholders have the information they need to make decisions when faced with an inability to meet demand.

At minimum, this responsibility includes providing public notification of all anticipated or actual drug shortages as well as discontinuations on www.drugshortagescanada.ca and participating in discussions with distributors, provincial and federal governments, and other key stakeholders throughout the shortage, consistent with the *MSSC Drug Shortages Protocol for the Communication and Notification of Drug Shortages*. In addition, other strategies should be incorporated into business practices such as:

- ***Releasing local supply status reports***, which can be used to communicate directly to health care providers and pharmacists any anticipated back orders within a given timeframe (e.g., 90 days) or as soon as an impending backorder is known.
- ***Providing advance notification*** of product discontinuation or supply disruption directly to supply chain stakeholders (wholesalers, distributors, health authorities, provinces, retailers, physicians and patients), particularly in a sole supplier situation.
- ***Adhering to an internal standard operating procedure***, which delineates roles and responsibilities for communicating details and lessons learned about the shortage to internal and external stakeholders.
- **Entrench corporate responsibility** by providing reliable information, working with the regulator and other stakeholders to resolve shortages, fostering a positive corporate attitude among all staff to produce safe, consistent and reliable pharmaceuticals.

Recommendation 13
Take a leadership role during shortages to ensure stakeholders have the information they need to make informed decisions.

5. RECOMMENDATIONS FOR DRUG MANUFACTURERS

In order to reduce the frequency and severity of drug shortages on the Canadian healthcare system and patients, wherever applicable, manufacturers should aim to implement the following industry recommendations within their manufacturing supply chain. To see how these recommendations align with the identified manufacturing risks, see Appendix A.

Appendix A – Alignment of Recommendations and Manufacturing Risks

Best Practices \ Manufacturing Risks	Raw material delays	Raw material QA failures	Importing issues	QA failures	No alternate manufacturing options	Packaging errors	Packaging shortages	Transport issues	Importation delays	License delays	Unforecasted demand increase	Business decisions	Regulatory disruptions
1. Alternative vendors	✓	✓		✓		✓							✓
2. Frequent on-site audits		✓		✓	✓	✓							✓
3. Comprehensive quality requirements		✓	✓	✓	✓	✓		✓	✓	✓			✓
4. Real-time communication systems	✓	✓			✓								✓
5. Supply chain analytics	✓	✓		✓	✓								✓
6. Investments in capacity and skills		✓	✓	✓	✓	✓		✓	✓	✓			✓
7. Adapt advanced quality assurance practices		✓	✓	✓	✓	✓		✓	✓	✓			✓
8. Improve demand and supply forecasting capability					✓						✓	✓	
9. Upgrade inventory tracking systems			✓		✓						✓		
10. Product-specific inventory allocation					✓						✓	✓	
11. Pre-qualify or contract with alternative sub-contractors	✓	✓	✓	✓			✓		✓	✓	✓		✓
12. Improve strategic market awareness					✓						✓	✓	
13. Leadership role during shortages	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Appendix B – List of Contributors

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