Multi-Stakeholder Toolkit

A Toolkit for Improved Understanding and Transparency of Drug Shortage Response in Canada

Revised in 2017

MULTI-STAKEHOLDER TOOLKIT

FOREWORD

The Multi-Stakeholder Steering Committee on Drug Shortages (MSSC) was assembled in 2012. The MSSC 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 drug shortages are a complex, global problem involving all stakeholders across the drug supply chain.

The Multi-Stakeholder Toolkit (Toolkit) describes the Canadian drug supply chain (including pharmaceuticals, biologic drugs and vaccines), 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. The Toolkit is a reference to support coordinated multi-stakeholder efforts to identify, mitigate, resolve and prevent drug shortages in Canada.

By clarifying roles, responsibilities and relationships, the Toolkit provides an important resource in understanding and mitigating drug shortages in Canada. It has been developed in conjunction with the MSSC *Protocol for the Notification and Communication of Drug Shortages* (Protocol). The Protocol sets out a tiered process for the notification and communication of information in anticipation of or response to a drug shortage with the potential for a significant impact on patient care in Canada. Together, the Toolkit and Protocol establish the understanding and expectations for coordinated multi-stakeholder notification, information-sharing and action to prevent, mitigate and manage drug shortages in Canada.

This document was prepared by MSSC members, with input from the Provincial/Territorial (P/T) Drug Shortage Task Team, the Multi-Stakeholder Working Group comprised of industry and health care associations as well as a number of regional health authorities, health regions, and other healthcare centres. It was updated in 2017 to reflect the Government of Canada's introduction of the *regulations on mandatory drug shortage and discontinuation reporting*. The complete list of contributors is available in Appendix A.

This Toolkit is intended to be a living document, open to ongoing revision and update as both the landscape surrounding, and the responses to drug shortages in Canada continue to evolve.

Quebec has collaborated in the multilateral efforts to strengthen notification and communication methods and to identify the best strategies for managing and preventing drug shortages, but it intends to retain control over the implementation of measures it deems appropriate with respect to drug shortages.

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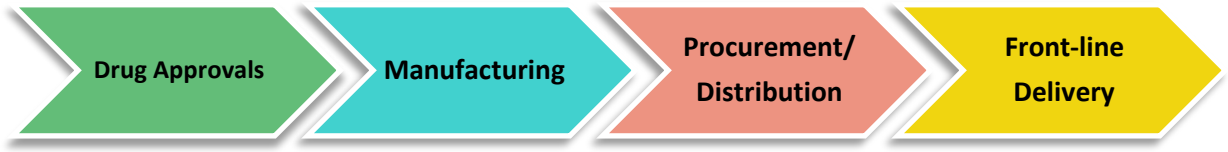
1. THE DRUG SUPPLY CHAIN IN CANADA

This section examines the complex drug supply chain by breaking it down to its key stages.

The total system can be divided into four major phases:



1.1 Drug Approvals

Manufacturers are responsible for producing safe drugs that are well researched and tested. As Canada's drug regulator, *Health Canada* (HC) authorizes applications for clinical trials of new chemical pharmaceuticals and biologic drugs; reviews results of these studies as well as extensive data on drug[1] safety, effectiveness and quality; and if approved, permits the *manufacturer* to market the drug in Canada.

Research for new drugs begins with the development of various chemical or biological substances. If preclinical tests indicate a substance produces the desired result with acceptable toxicity levels, the sponsor (i.e., the person or company who takes responsibility for the application) will apply for authorization to conduct a clinical trial.

The purpose of clinical trials is to research and gather information on a drug's dose, effectiveness and safety in humans. Prior to the commencement of a clinical trial in Canada, HC reviews a clinical trial application. This application requests permission to distribute the drug to responsible clinical investigators named in the application.

If clinical trial studies demonstrate the drug has potential therapeutic value that outweighs associated risks (e.g., adverse effects, toxicity), the sponsor may choose to file a New Drug Submission with HC. The following list specifies the steps in the drug approval process.

a) A sponsor files a "New Drug Submission" containing information and data about the drug's safety, effectiveness and quality. It also includes the results of the preclinical and clinical studies, details regarding the production of the drug, packaging and labeling details, and information regarding therapeutic claims and side effects.
b) HC performs a thorough review of submitted information, sometimes using external consultants and advisory committees.
c) HC evaluates safety, efficacy and quality data to assess potential drug benefits and risks.
d) HC reviews information the sponsor proposes to provide to health care practitioners and consumers about the drug (e.g., label, product monograph).
e) If the review concludes that the benefits outweigh the risks, and the risks can be mitigated, the drug is issued a Notice of Compliance (NOC), as well as a Drug Identification Number

[1] For the purposes of the Toolkit, the term "drug" refers to all prescription pharmaceuticals and biologic drugs, including vaccines (excludes blood and blood components and other tissues and organs).

(DIN),[2] permitting the sponsor to market the drug in Canada and signifying the drug's official approval in Canada.

f) In order to monitor safety, efficacy and quality, HC laboratories may test certain biological products before and after authorization to sell in Canada has been issued, through the Lot Release Process.

1.2 Manufacturing

Manufacturers of approved drugs include fabricators, packagers/labellers, and testers. Manufacturing may include several processes such as chemical synthesis, fermentation, distillation and solvent extraction; grading, grinding and milling; and packaging in forms suitable for internal and external use (e.g., tablets, vials, creams and ointments). All drug manufacturing in Canada must meet applicable Good Manufacturing Practices (GMP) as set out in the *Food and Drugs Act* and *Regulations (F&DA/R)*, enforced by *HC*.

There are two major phases of pharmaceutical production: 1) the active pharmaceutical ingredient (API) is manufactured; and 2) the API is processed and converted into an administrable form (e.g., injectable, tablets, capsules, liquids, ointments, or creams).

The manufacturing process for biologic drugs is more variable due to the use of living microorganisms, animal and/or plant cells. While the end product of a pharmaceutical can be easily tested for purity and quality, biologic drug consistency, purity and quality must be ensured by the manufacturing process and numerous process controls. Biological source materials, production cells or fermentation media could present risks such as initial presence of pathogens or viruses. Minor changes in the manufacturing process or source materials can have unexpected effects on the end product and its functions. In general, the lead time to manufacture, package, distribute and test (validate) vaccines ranges from 6-24 months.

Manufacturing processes for pharmaceutical and biologic drug products are regulated under the F&DA/R. In addition to receiving a NOC and DIN, the manufacturer must also apply for an Establishment License signifying that they meet Canadian GMP standards related to fabrication, packaging/labelling, distributing, importing and testing.

Establishments that are found to be non-compliant with regulatory requirements must take necessary and timely corrective action to bring operations into compliance. Evidence must be provided of their commitment to comply with GMP requirements and a written plan of corrective action must be submitted. Compliance is normally achieved through a cooperative approach between the regulated party and HC. However, when the regulated party is unable to correct non-conformities, several enforcement options may be used, including the suspension of an establishment license.

Finally, most foreign countries that import drugs for human use require the manufacturer to comply with jurisdictional regulations related to GMP. As a result, foreign inspectorate agencies

[2] Health Canada's Drug Product Database (DPD) contains product specific information on drugs approved for use in Canada. The database is managed by Health Canada and includes human pharmaceutical and biological drugs, veterinary drugs and disinfectant products. It contains approximately 15,000 authorised products which companies have notified Health Canada as being marketed.

routinely inspect Canadian manufacturing facilities to ensure compliance with their jurisdictional requirements.

1.3 Procurement and Distribution

Procurement and Distribution captures the movement of final products from the manufacturer to the front line user. Most drug distribution in Canada is indirect – i.e., through *wholesalers, distributors and importers*. These companies aim to consolidate ordering, purchasing and delivery of drug products and act as intermediaries between manufacturers and front line delivery organizations.

Group purchasing organizations negotiate buying contracts to secure cost savings for regional health authorities (RHAs) and hospitals. *Wholesalers and distributors* work directly with pharmacies by purchasing, selling, and distributing products through various ordering mechanisms. *Importers* generally import drug products from foreign sites for distribution and sale in Canada. Under certain circumstances, the *federal government* procures select medications for emergency preparedness. Further, the federal government negotiates contracts for vaccines and drugs on behalf of provinces/territories (P/Ts) through a formal consensus-based process.

All drug wholesaling, importation and distribution activities require a valid Establishment License related to GMP standards under the F&DA/R. Further, all foreign sites which fabricate, package/label and test drugs for the Canadian market are to be included on the importer's establishment license. HC inspects facilities to assess whether the firm meets regulatory requirements on a number of categories such as premises, personnel, transportation, records and standard operating procedures.

P/Ts do not normally purchase drug products directly (exception: see below for vaccine supply). However, in an effort to achieve better value for generic drugs, Canada's premiers at the Council of the Federation recently supported a plan to price-set six generic prescription drugs. Participating provinces and territories have agreed to establish a price point for six of the most common generic drugs at 18 per cent of the equivalent brand name drug. The new prices were in effect as of April 1, 2013.

With respect to vaccines, the National Immunization Strategy was developed in 2003 to provide a comprehensive federal/provincial/territorial (F/P/T) strategy and collaborative approach to address vaccine supply and achieve best value for vaccine procurement, long-term security and quality of supply. The Vaccine Supply Working Group (VSWG) (supported administratively by the Public Health Agency of Canada (PHAC) and includes all jurisdictions) makes consensus-based vaccine supply contracting decisions, which are then negotiated by Public Services and Procurement Canada (PSPC) on behalf of all participating P/Ts and federal clients (Department of National Defense [DND], Correctional Service of Canada [CSC], Royal Canadian Mounted Police [RCMP] and HC). This allows all jurisdictions to take advantage of the best prices and contract conditions; to improve security of supply; and to access collective benefits, such as alternate suppliers if needed.

1.4 Front Line Delivery

The drug supply chain is designed to deliver drugs to patients. Front line delivery organizations include *hospitals, pharmacies, and other health care facilities*. *Patients* are in direct contact with health care providers who prescribe drugs and biologics based on unique patient needs, provide

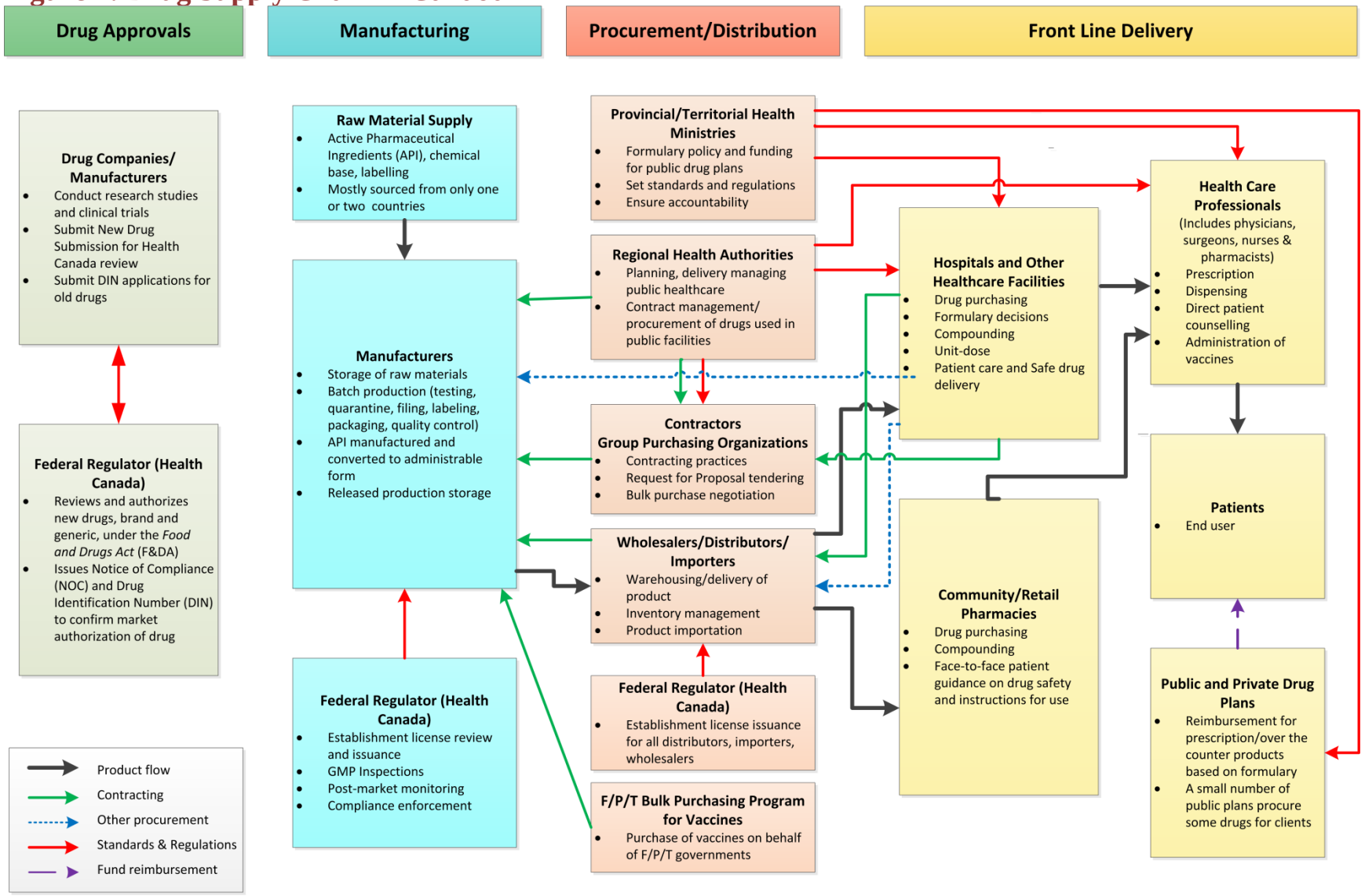
information on drug indications, contraindications, interactions and alternatives, and provide guidance on safety and instructions for use. Hospitals and long-term care facilities provide care and treatment to their patients and outpatients. Pharmacies dispense prescription and non-prescription medications directly to the patient or caregiver. Drugs are acquired through the procurement/distribution network discussed in the previous section.

Under the *Canada Health Act*, most drugs administered to inpatients and outpatients are fully funded by the public healthcare system. Hospital formulary decisions are made by each hospital, often in consultation with their RHA. Hospital budget decisions are made by the P/T Ministries of Health and RHAs. Each province and territory and a small number of federal departments provide publicly funded drugs for specific populations. Formularies for each of these public insurance plans are determined by the provider.

Health services and medications used outside the publicly funded healthcare system can be funded through a private insurance health plan. Insurance plans are commonly offered through an employer benefits package; alternatively, coverage can be individually sought through a third-party insurance provider or paid out-of-pocket.

Figure 1 presents a visual depiction of the Canadian Drug Supply Chain.

Figure 1: Drug Supply Chain in Canada



2. Roles and Responsibilities of Key Players

Drug shortages can originate at any point in the supply chain; for example, from production or market issues, surges in demand, difficulties obtaining raw supplies, or natural disasters almost anywhere in the world. As a consequence, all stakeholders in the supply chain have important roles to play in safeguarding the Canadian drug supply. The following section provides a brief description of the roles and responsibilities of each of these stakeholders. Stakeholder strategies and tools specific to an actual shortage are set out in Section 3.

2.1 Manufacturers

Chemical pharmaceutical drug (brand name and generic) and biologic drug manufacturers supply HC approved medicines to meet the demand of the Canadian market. Manufacturing facilities and product quality must comply with regulatory requirements set out by the F&DA/R, including GMP standards and Establishment Licenses (EL). HC conducts risk-based inspections of Canadian facilities to ensure that these procedures and standards of practice are compliant with Canadian regulations.

To adapt to changing market demands, manufacturers maintain extensive knowledge of current and evolving supply and demand fluctuations related to their specific products. Capacity to manage reasonable demand fluctuations in the marketplace are often built into operating and production/planning procedures. As such, individual companies may adjust supply to the market, depending on individual market share at the time of demand fluctuations, thereby preventing a shortage.

According to domestic and international trends, the causes of drug shortages are often related to manufacturing processes (e.g., equipment malfunction and validation, raw material supply delays, post-production product quality or sterility, import and transport delays), increases in demand resulting from other product shortage, or errors in forecasting market demand.

2.2 Group Purchasing Organizations

Group Purchasing Organizations (GPOs) act as intermediaries between manufacturers/suppliers and their member organizations, mainly hospitals and RHAs. Negotiating directly with manufacturers on behalf of many buyers through a request for proposal (RFP) process, GPOs secure lower prices through bulk purchasing. With respect to drug shortages, bulk purchasing has become the focus of increasing scrutiny, especially when relying on sole suppliers.

GPOs may also support collaboration among key stakeholders in preventing and managing drug shortages. Ongoing market research and direct communication with manufacturers and buyers have helped GPOs advance preventative action through the development of new drug procurement strategies such as split award contracts.

2.3 Distributors/Wholesalers/Importers

Pharmaceutical distribution, importation and wholesaling include the purchase, sale, importation, warehousing, storage, order preparation, and delivery of an assortment of medical products and drugs to meet the needs of community pharmacies, hospitals, long-term care centres, clinics, and

other healthcare institutions. Most large pharmaceutical distributor/wholesaler companies have distribution centers located across the country to service various geographical areas.

Pharmaceutical wholesalers procure products directly from drug manufacturers and importers and sell them to pharmacies in Canada (about 90% of volume to community pharmacies, 10% to hospital pharmacies). They consolidate shipments to pharmacies to achieve efficiencies and control costs. Importers and wholesalers may also be required to manage returns and recalls and hold returned products in their inventories until expiry.

During a drug shortage, wholesalers/distributors may help monitor and communicate stock levels, and manage equitable distribution of drugs to pharmacies through the proportional allocation of remaining stocks

2.4 Provinces/Territories

P/Ts set policy and direction to achieve a sustainable and accountable health system, and to promote and protect the health of residents. Within provinces and territories, the logistics of contracting, ordering and distributing drug products are handled by RHAs, hospitals, GPOs, wholesalers, distributors and community pharmacies.

P/Ts each provide some form of assistance for the purchase of prescription drugs. Government-sponsored insurance programs vary by jurisdiction; however, they most often include coverage for senior citizens, social assistance recipients, and population groups with specific diseases. Formulary decisions in each jurisdiction are supported by the "Common Drug Review" (CDR) process (except in Quebec) which is led by the Canadian Agency for Drugs and Technologies in Health (CADTH). The CDR process reviews the clinical and cost-effectiveness evidence and patient input for drugs, reducing duplication of reviews by jurisdictions.

During an actual or anticipated drug shortage of national significance, P/Ts may work with HC to facilitate discussions between manufacturers and front-line delivery organizations (RHAs and hospitals). These discussions have been used to highlight the critical importance of timely, regular, accurate and complete information about actual shortages, supply and production status, allocation rates, and re-supply dates. P/Ts may also act as intermediaries with industry associations (Innovative Medicines Canada and the Canadian Generic Pharmaceutical Association [CGPA]) and health professional associations(Canadian Pharmacists Association).

While the purchase of most drugs does not fall under the direct purview of P/Ts, these governments do purchase certain vaccines, drugs and antivirals to prevent and control infectious diseases as part of their health mandate. To facilitate procurement and supply management, P/Ts work collaboratively with federal partners through the VSWG and the F/P/T Bulk Purchasing Program (BPP) for Vaccines. The VSWG's mandate includes representing the P/Ts in consensus-based vaccine purchasing decisions under the BPP and specifying contract terms and conditions. It should be noted that P/T participation in the BPP is voluntary. For more details on this process, see "Other Federal Departments" below as well as section 3.3.

2.5 Regional Health Authorities

RHAs deliver public healthcare services to residents in provinces and territories. Some smaller P/T jurisdictions, and Alberta, have one single health authority serving the entire province or territory.

The majority of jurisdictions have a number of RHAs, typically based on geographic boundaries and population density.

Under P/T legislative authority, RHAs are responsible for the planning, delivery, management, monitoring and evaluation of public health services. Most oversee a variety of facilities (e.g., hospitals, acute care clinics, continuing care facilities, mental health facilities and community health sites). They commonly collaborate with P/T health ministries and provide input on P/T health policy development and planning.

Most RHAs play a lead role in the contract management and procurement of drugs used in facilities in their regions. RHAs currently identify key critical medications and maintain increased inventory. In times of shortage, RHAs have the ability to reallocate stock among facilities within the region or province.

2.6 Hospital Pharmacies & Pharmacists

Hospital pharmacies are responsible for the procurement of drug products as well as ensuring the product is in a ready-to-administer form for patients (both inpatient and outpatient). Hospital pharmacists provide care directly to patients and work within the healthcare team to optimize medication management for patients. They also support in-facility formulary decisions, and provide drug information to healthcare practitioners. Hospital pharmacists work with pharmacy technicians to develop drug policies and procedures on medication procurement and use, compound and repackage (sterile and non-sterile) preparations, dispense drugs, and oversee the drug distribution and safe handling from point of entry to the patient. During a drug shortage, hospital pharmacists consult with medical stakeholders to identify conservation strategies and/or alternative drug treatments for patients.

Hospital pharmacies are accountable for managing pharmaceutical procurement, including participating in contracting decisions though GPOs and Shared Service Organizations (where applicable).

2.7 Community Pharmacies & Pharmacists

Community pharmacies serve patients directly through one-on-one health care service provision and medication management. This includes traditional pharmacist roles (e.g., compounding and dispensing prescription drugs, educating patients about their prescription and non-prescription medications), and evolving patient-centred medication management services (e.g., providing detailed drug information, patient-specific medication reviews and medication history, clinical advice, prescribing in the presence and the absence of a medical prescription; ordering and interpreting lab tests; administering a drug or a vaccine by injection).

Community pharmacists are central to managing patient care during a drug shortage. They communicate with various sources to identify available products, liaise with physicians to determine alternative care, and directly counsel patients on substitute drug therapies.

2.8 Health Care Professionals

Health care professionals (e.g., physicians, pharmacists, and nurses) play an important role in promoting appropriate drug use. To provide the public with information on the risks and benefits of specific drugs, health care professionals rely on HC and drug manufacturers to disseminate accurate, up-to-date safety and usage information. If a therapy is unavailable during a shortage, health care professionals may determine suitable alternatives.

Health care professionals monitor the continued safety of approved drugs. They are often the first to become aware of serious adverse drug reactions, making health care professionals a critical source of safety information and key contributors to the evolving knowledge of a product's risks and benefits. This is particularly imperative during a shortage, where patients may be faced with using alternative therapies, newly market authorized drugs or, under extraordinary circumstances, unapproved drugs.

2.9 Federal Government

Health Canada

As the federal regulator, HC reviews drug submissions for safety, efficacy and quality as required by the F&DA/R. HC is the Canadian federal authority that regulates the sale of pharmaceutical drugs, medical devices, and biologics (e.g., blood, tissues and organs) for human use. Prior to market authorization, a manufacturer must present HC with substantive scientific evidence of a product's safety, efficacy and quality. Upon review of the evidence, HC determines if the benefits of the product outweigh its risks, and whether the risks can be mitigated.

HC is responsible for compliance and enforcement activities, including conducting inspections, and assessing conformity to standards related to the fabrication, packaging/labelling, testing, importation, wholesaling and distribution of marketed health products for human and veterinary use as well as compliance and enforcement of the new mandatory reporting of drug shortages and discontinuations.

As the federal regulator, HC has a number of tools and strategies available to assist companies and manufacturers in minimizing the impact of a supply disruption. HC works with manufacturers to review alternate suppliers, changes in manufacturing processes, or changes in manufacturing locations, when necessary.

Other Federal Departments

To supplement the extraordinary needs of P/Ts in times of critical emergency – such as a mass casualty event or a pandemic –PHAC maintains a limited supply of select drugs in the National Emergency Stockpile System (NESS). When manufacturers and/or healthcare facilities cannot meet urgent medical supply needs, PHAC can enable emergency access to products or alternatives.

The Government of Canada, through various programs, provides drug coverage for over one million Canadians who are members of eligible groups, including: First Nations and Inuit; members of the military; veterans; members of the RCMP; eligible refugees; and inmates in federal penitentiaries. The federal government also represents Canadian interests in international fora such as the World Health Organization (WHO) and the Organisation for Economic Co-operation and Development (OECD), and partners with international regulatory counterparts to assess and prevent the global cause of drug supply disruptions.

On behalf of F/P/T governments, PSPC manages the F/P/T Bulk Purchasing Program (BPP) for Vaccines. The BPP works with P/Ts, as well as the federal CSC, DND, the RCMP and HC to acquire a

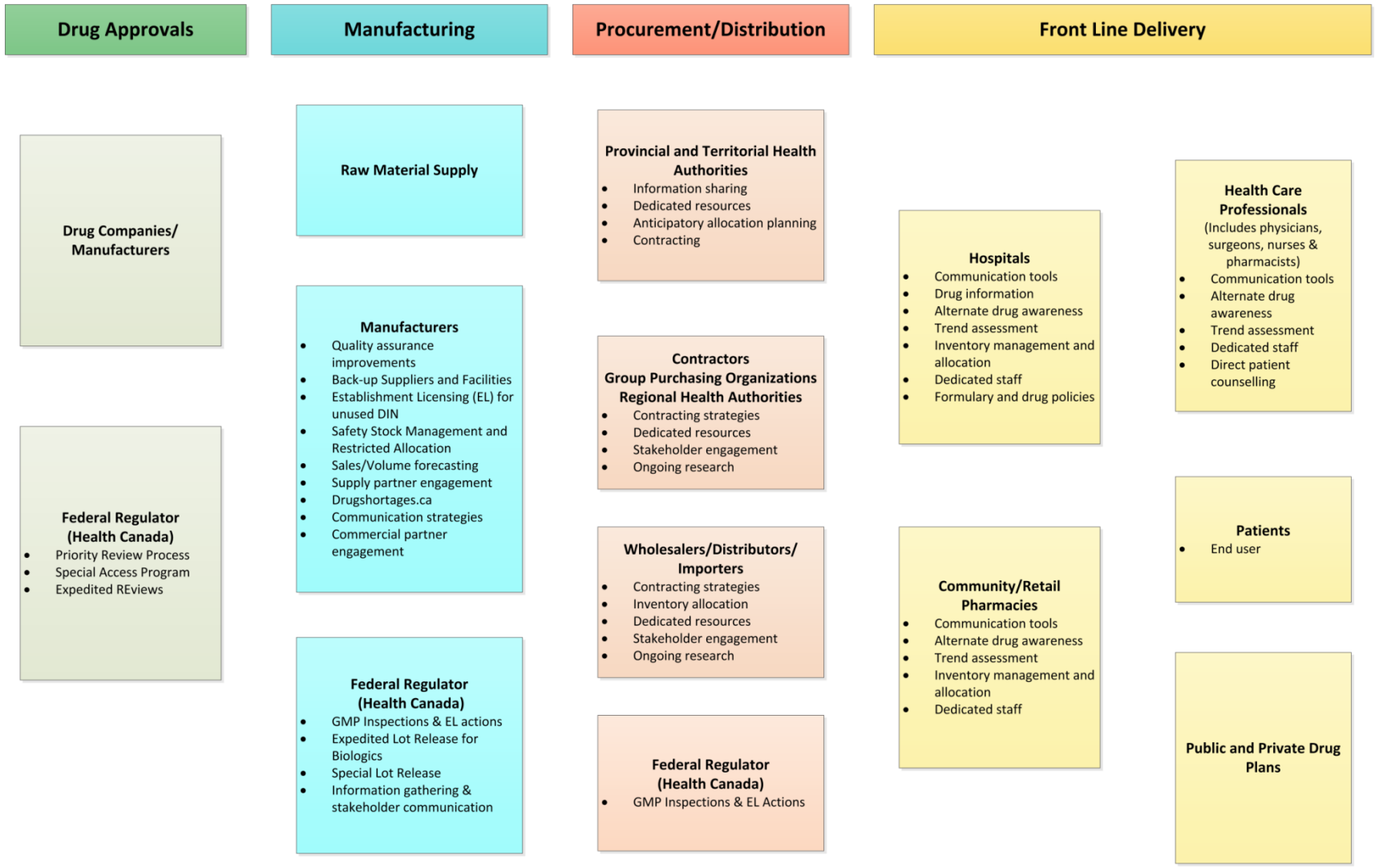
safe supply of vaccines (and some drugs) for Canadians. The BPP purchases the annual influenza vaccine, approximately 51 other vaccines, and a variety of drugs, including antivirals. Contracting decisions are overseen by the VSWG – a multi-jurisdictional group that monitors vaccine supply and prices, and develops principles, guidelines and strategies for addressing vaccine supply issues, such as vaccine shortages.

3. DRUG SHORTAGES: STRATEGIES AND TOOLS

This section describes the activities and interaction of key players in each link of the drug supply chain, including causes of drug shortages; and drug shortage strategies and tools.

Figure 2 presents a visual overview of drug shortage tools at each stage of the supply chain.

Figure 2: Overview of Drug Shortage Tools and Strategies



3.1 Drug Approvals

Key players: Drug manufacturers, federal regulator (Health Canada)

3.1.1 Causes of Drug Shortages

Drug shortages seldom originate at the drug approval stage as the drugs are *pending* approval for sale in Canada. An exception would include cases whereby a manufacturer makes changes to an already-authorized product through a Supplemental New Drug Submission. If the data submitted to HC is insufficient or incomplete, this could lead to delays in return to production until all approvals are obtained.

3.1.2 Drug Shortage Strategies and Tools

While narrow in scope, and not specifically intended to address drug shortages, HC, in consultation with manufacturers and physicians, does have three primary tools to employ at the drug approval stage to help mitigate the impact of significant shortages.

Drug Product Database (DPD). Health Canada's DPD contains product specific information on drugs approved for use in Canada. The database is managed by Health Canada and includes human pharmaceutical and biological drugs, veterinary drugs and disinfectant products. It contains approximately 15,000 authorised products which companies have notified Health Canada as being marketed. The DPD can be used to identify alternative products that may be available in the Canadian market.

Expedited Review Process. While not a specific authority outlined in regulation, the expedited review process is a discretionary tool HC can use to expedite the review of a drug submission to enable access to, for example, an alternative drug during a shortage. Expedited Reviews do not require a written request from the sponsor.

Special Access Program (SAP). SAP provides physicians access to non-marketed drugs for treating patients with serious or life-threatening conditions when conventional therapies have failed, are unsuitable, or unavailable. The SAP authorizes a manufacturer to sell a drug that cannot otherwise be sold or distributed in Canada. Drugs considered for release by the SAP include pharmaceutical, biologic, and radio-pharmaceutical products.

In a serious shortage situation, SAP could provide access to drug alternatives if (1) the drug in shortage is indicated for a serious or life-threatening condition, (2) there are no other reasonable alternatives on the Canadian market, and (3) if the sponsor affected by the shortage has demonstrated reasonable and extraordinary efforts to manage the shortage and has a strategy with solid timelines to resolve the problem. In most circumstances, SAP provides access to products that are manufactured at a facility in a different jurisdiction (e.g., foreign sites).

3.2 Manufacturing

Key players: Manufacturers, raw material suppliers, federal regulator (Health Canada)

3.2.1 Causes of Drug Shortages

Many drug shortages arise in the manufacturing stage. If the manufacturer cuts back, delays, temporarily ceases, or discontinues the production of a drug it may cause a disruption or shortage in supply. Shortage severity may be more significant when the drug in question is produced by only one manufacturer and for which there are limited (or no) therapeutic alternatives. Below is a list of the most common causes of drug shortages originating at the manufacturing stage:

- **Non-compliance with standard manufacturing processes** resulting in product recalls. Non-compliance with manufacturing or regulatory standards can lead to immediate production shutdowns, requiring potentially lengthy manufacturing updates (e.g., production line modifications).
- Foreign inspections and **non-compliance of foreign suppliers** (or local manufacturers) with foreign regulatory requirements can result in unanticipated drug shortages in Canada. Resulting shut-downs of foreign manufacturers may cause shortages in the Canadian market.
- The majority of manufacturers in Canada use **single source foreign suppliers** for raw materials. Many manufacturers source these materials from the same suppliers. When raw material supply is halted in an international jurisdiction for any reason (e.g., non-compliance with GMP standards, political unrest, natural disasters) the local manufacturer(s) is confronted with a lack of necessary supply.
- In most production facilities, even minor **changes in manufacturing procedures** or production lines cause a temporary reduction or stoppage of manufacture of products. In many cases, facilities require regular upkeep and maintenance and are able to prepare for this temporary disruption by proactively increasing production. However in some instances, unanticipated stoppages do occur.
- **Global economic trends** see fewer manufacturers producing drugs for increasing market demand. Corporate mergers and acquisitions (particularly in generics) lead to fewer manufacturers and business decisions that increase the risk for drug shortages, such as: discontinuance of products that are no longer profitable; downsizing product portfolios; and the addition of new products which limits the capacity to continue manufacturing the same volume of existing products.
- Unanticipated **increases in demand** resulting in insufficient quantities to meet actual/anticipated needs.
- Inconsistencies in **international regulatory requirements** (e.g., labelling) can make importing foreign-made products difficult in times of shortage.

3.2.2 Drug Shortage Strategies and Tools

<u>Manufacturers</u>

Quality Assurance. Many manufacturing firms have enacted rigorous quality standards to support continuous improvements to production practices and improved quality control outcomes.

Back-up Suppliers and Facilities. As the risk of API and raw material supply shortages become more common, manufacturers are beginning to identify alternate sources of supply in the event the primary supplier cannot meet demand. In addition, back-up manufacturing sites, packing, and packaging components are being identified and utilized more often.

Establishment Licensing for Unused DIN. Occasionally manufacturers who received a DIN through the drug approval process do not actively produce the drug. In the event of a drug shortage, manufacturers may choose to modify their facilities to accommodate the production of unused DIN-approved drugs to meet market demands. Relevant F&DA/R review and approvals related to GMP and Establishment Licensing requirements would be required prior to market authorization.

Safety Stock Management and Restricted Allocation. As a preventative measure, some manufacturing firms hold a reserve supply of products with a higher-risk of shortage. This may assist short term allocation schemes in the event of a disruption or shortage. However, in the event of a shortage, more aggressive allocation strategies are sometimes used, which includes restricting allocation to contract holders only.

Sales/Volume Forecasting. Increased coordination between sales and operations is employed to determine reliable sales forecasts.

Supply Partners. Manufacturers conduct periodic reviews with external parties (e.g., contracting parties, distributors, purchasers) regarding current supply levels, scenario planning, impact of changing demand, and identification of potential risks that can affect regular product supply.

www.drugshortagescanada.ca is the key drug shortage notification and information tool for stakeholders across the drug supply chain. Since 2012, industry associations have been administrating the voluntary drug shortage reporting website, www.drugshortages.ca. In 2016, HC introduced new regulations which require drug manufacturers to report drug shortages as well as discontinuations on ***www.drugshortagescanada.ca***. The timely, reliable and comprehensive posting of all anticipated and actual drug shortages by manufacturers, and posting of information on the return to market date, drug specifics, shortage cause, etc., is essential in ensuring coordinated and appropriate responses to drug shortages.

Communication Strategies. In the event of an anticipated or actual shortage, some manufacturers have implemented a communication plan to address how the distribution of remaining product will be prioritized and allocated. Communication is directed to all relevant stakeholders, including other manufacturers of the same product or known therapeutic alternatives.

Business Continuity Plan. Some manufacturers ensure all vendor and distribution partners have a Business Continuity Plan (BCP). BCPs help to minimize long term disruption in supply as well as proactively monitor stock-in-trade with wholesalers.

Alternatives. Manufacturers may locate alternative manufacturers and/or alternative therapies to temporarily ease short term demand disparities.

Health Canada (F&DA/R)

GMP Inspections and Establishment Licence (EL) Actions. A drug shortage resulting from a manufacturing or facility issue requires immediate intervention by an HC Drug Inspector to understand the root cause and monitor any planned remediation or corrective actions. Depending on the severity of the production issue, HC has a number of EL decisions that can be exercised based on risk assessments and lab testing (i.e., recall, stop sale, licence amendment or revocation).

If a non-compliance enforcement action is likely to cause significant negative effects on the health system, enforcement discretion *may* be used to assess the risks and benefits of varying responses.

Mutual Recognition Agreements. Canada is a participant to Mutual Recognition Agreements (MRAs) covering GMP Compliance Programmes related to medicinal products. The MRAs are based on demonstrated equivalency of the inspectorate programs, (i.e., Canada and the other party have equivalent GMP compliance programmes). Hence, a Certificate of Compliance is accepted as evidence of GMP compliance in lieu of an actual inspection. Agreements with trusted regulatory counterparts allow for faster authorization of alternate international manufacturers by pre-determining the safety, efficacy and quality of their regulated manufacturing processes; thereby allowing the temporary importation of equivalent quality drugs not currently marketed in Canada. While MRAs do not include harmonization of standards and drug regulations, they provide opportunities to develop closer and stronger relationships with other regulatory authorities.

Expedited Lot Release for biologic drugs. Each lot of a biologic drug is subject to the Lot Release Program, and requires a formal HC Release Letter before sale in Canada. The targeted timeframe for products to be released is 6 weeks after receipt of all required information and samples; however, *expedited release* may be granted in exceptional cases and upon appropriate justification (such as product shortage in Canada). The risk-based Lot Release Program covers both pre- and post-market stages.

Special Lot Release. Under certain circumstances, HC may approve the sale of drug products being produced by a manufacturer not licenced in Canada (i.e., foreign manufacturer), to ease the effects of a shortage. In these cases, HC Drug Inspectors will assess the GMP compliance with Canadian GMP standards before approving market authorization.

Drug Approval tools. Drug shortages caused by manufacturing issues or business decisions may necessitate access to alternate therapies through the drug approval stage of the supply chain. For HC's tools at this stage, see Section 3.1.3.

Information Gathering and Stakeholder Communication. During a national drug shortage, it is critical that accurate information on affected products and dosages, status of the shortage, and estimated return of supply, etc., be communicated to the drug supply chain stakeholders in a timely manner. While the primary responsibility for timely, accurate and fulsome communication rests with the manufacturers, other parties such as the P/T Task Team on Drug Shortages, HC and PHAC (e.g. through the Health Portfolio Emergency Operations Centre) support P/Ts and other stakeholders to coordinate the validation and dissemination of pertinent information. ***Mandatory Reporting Regulations.*** Mandatory drug shortage and discontinuation reporting enables HC to provide timely, reliable and accurate information to the public as well as to provide healthcare professionals, patients, drug supply stakeholders, and P/T governments with the information they require to mitigate and manage effects of drug shortages.

In addition, as part of its regulatory responsibilities, HC is responsible for compliance and enforcement activities in order to verify that regulatory requirements are being applied appropriately.

For further information on the coordination of notification and communication, see the *MSSC Protocol for the Notification and Communication of Drug Shortages.*

3.3 Procurement and Distribution

Key players: GPOs, Wholesalers, Distributors, Importers, RHAs, P/T Governments

3.3.1 Causes of Drug Shortages

Recent shortages have highlighted two key weaknesses in the procurement and distribution stage of the supply chain:

- **Sole sourcing** of products from one manufacturer on behalf of many buyers introduces vulnerability to the overall supply chain when the sole supplier halts or delays production. Sole sourcing also limits new market entrants and may price alternate manufacturers out of the market completely; further reducing supply source options in the future.

- **Inventory management** practices (e.g., "just-in-time" schemes) may diminish stability when unexpected increases in demand cannot be met with current stock; resulting in disproportionate pressure on remaining manufacturers to alter production in order to fulfill sudden market needs.

3.3.2 Drug Shortage Strategies and Tools

GPOs, Wholesalers, Importers and Distributors

Contracting strategies. Large GPOs may incorporate split award and multiple vendor procurement strategies to improve access to supply while preserving market competition. This approach provides an opportunity for future new market entrants to have access to contracts, further mitigating risk associated with relying on too few suppliers. Contracts can require manufacturer contingency plans for occasions when they are not able to meet demand.

Inventory allocation. Using limited stocks, wholesalers/distributors are able to allocate remaining inventory based on buyer needs and specific circumstances. Typically, on-hand stocks do not last beyond two to three months. However, if a suitable therapeutic alternative is identified, wholesalers/distributors can act quickly to secure supplementary stock insofar as manufacturers are able to meet increased demand. In the event of suspected hoarding of drugs at-risk of shortage, the wholesaler/distributor may work directly with the buyer to arrive at a balanced solution.

Dedicated resources. Many contracting and distribution firms have dedicated specialized staff (e.g., pharmacists) to exclusively manage drug shortages on a partial or full-time basis. These individuals work with suppliers and clients to initiate and implement proactive and reactive strategies that will help prevent and/or minimize the impact of drug shortages.

Stakeholder engagement. Ongoing communication amongst clients, manufacturers and government representatives plays an important role during shortages; as well as a tool used for prevention by communicating and learning from best practices. Regular engagement is achieved though news bulletins, website updates, seminars, and face-to-face meetings.

Ongoing research. Many firms investigate market and drug shortage trends to gather lessons learned and best practices, and inform strategies to prevent and mitigate future shortages.

Regional Health Authorities, hospitals and P/T Governments

Information sharing. In many P/Ts, critical information during a shortage is shared through ad-hoc and systematic networks. Various stakeholders are consulted using teleconference and face-to-face meetings. Often, coordinated teams work together to review stakeholder inventory reports, disseminate critical updates, advise on appropriate allocation strategies, develop clinical contingency plans, and monitor status.

Dedicated resources. P/Ts, RHAs and hospitals commit resources and primary contacts specifically to address drug shortages, building relationships and knowledge enabling more effective responses.

Anticipatory allocations. In anticipation of serious shortages, critical medications are identified in order to maintain sufficient inventory. This allows more equitable reallocation of stock within the region in an actual shortage situation.

Ethical Frameworks. Some P/Ts, as well as other organizations (e.g., University of Toronto, University of British Columbia), have developed ethical frameworks for resource allocation during drug shortages that are being incorporated into RHA and facility level shortage response strategies.

Vaccine Supply Stakeholders

Through the work of the multi-jurisdictional VSWG and the F/P/T BPP, a number of strategies have been adopted to reduce the frequency and severity of vaccine and antiviral shortages. Many of these approaches have reduced health disparities across the country through more equitable vaccine access.

Single "window" contract administration. Supply contracts for participating jurisdictions are negotiated through the BPP. This method reduces duplication of effort (i.e., need for individual tenders issued by P/Ts) and enhances security of supply. It also allows for early identification of potential supply issues and provides a mechanism for a coordinated response to supply issues.

Split award contracts. Under the BPP, most vaccines are supplied by multiple suppliers using split award contracting, thereby mitigating risks associated with sole sourcing.

Other contract clauses. Most contracts stipulate requirements for mandatory inventory stockpiles, and obligations for manufacturers to increase supply in the event of a disruption from other suppliers. These agreements usually require the supplier in shortage to provide for an alternative vaccine acceptable to users, and/or to cover any associated costs associated with a higher purchase price.

Guidance documents. The VSWG has developed guidance setting out principles, roles and responsibilities for minimizing and mitigating vaccine supply disruptions. The Group is also developing Standard Operating Procedures for biologics procured via the HC SAP.

Collaborative management. The VSWG provides a forum for information sharing and collaborative decision making to rapidly implement strategies for managing supply shortages. The VSWG advocates for the development of strategies to enhance security of supply (e.g., inclusion of stockpiles in contracts, greater acceptability of alternative products to broaden the supplier base requirement, etc.).

Coordinated action. In the event of a shortage, the VSWG drafts an allocation plan based on supplier input and Group consensus, to ensure remaining supply is equitably distributed amongst users. F/P/T partners report on their current inventory levels and estimated requirements from date of notice to expected shortage resolution date. Depending on nature and severity, the supply concerns may be elevated within the Pan-Canadian Public Health Network (e.g., Communicable and Infectious Disease Steering Committee, the National Advisory Committee on Immunization, or the Council of Chief Medical Officers of Health). Throughout this process, various coordinated communication tools are developed collaboratively by P/Ts, PHAC and HC.

3.4 Front Line Delivery

Key players: Community and hospital pharmacies, health care professionals (physicians, community and hospital pharmacists, etc.), Patients

3.4.1 Causes of Drug Shortages

As the final dispensers of drug products, healthcare professionals working within the front line delivery stage have limited control over cause and prevention of drug shortages. The availability of stock at the front line delivery stage is impacted by:

- **Inventory management strategies** used at community pharmacies, RHAs and drug wholesalers and distributors that minimize stock holdings (i.e., "just-in-time") result in little or no inventory cushion to address short-term shortages.

- **Stockpiling** by hospital and community pharmacies limits the potential to re-allocate inventory between facilities/regions, and has the potential to cause a secondary shortage if there is an incomplete picture of total stock available in the system.

- **Limited drug supply movement** between the community pharmacy supply chain and the acute supply chain of RHAs to re-allocate available stock during a shortage.

3.4.2 Drug Shortage Strategies and Tools

Communication. Improved communication channels amongst community pharmacies and inter-departmental health professionals, other facilities, RHAs (hospital pharmacies), P/Ts and distributors, facilitates the dissemination of information. Therapeutic publications provide additional information on products in short supply to front line delivery workers.

www.drugshortagescanada.ca is the key drug shortage notification and information tool for stakeholders across the drug supply chain, including front line delivery health care professionals. The timely, reliable and comprehensive posting of all anticipated and actual drug shortages is fundamental to preventing, mitigating and managing drug shortages, and is the primary tool for providing health care workers and patients the information they need to make timely, well-informed decisions.

Alternate drug awareness. Many front line agents pursue continuous research and consultations on shortage tools and strategies, including therapeutic alternatives, suitable formulations, equivalent concentrations and dosage strengths, forecast of at risk critical products, and non-market alternatives (i.e., to seek access through federal regulatory measures – when warranted).

***Trend assessments*.** Many front line facilities employ pharmacists who routinely assess utilization patterns and recommend action if the usage is unnecessarily high (which could be indicative of unnecessary/avoidable demand on a particular drug). Additionally, within RHAs and hospitals, the use of perpetual inventory systems and forecasting methods help identify stock-out dates in advance, particularly important for drugs at high risk of shortage due to limited sources.

Inventory management and allocation. In anticipation of, and reaction to drug shortages, (hospital pharmacies) calculate and control inventory volumes. In consultation with prescribers, forecasted needs are based on the most critical requirements while suitable alternative treatments (when available) are allotted to lesser cases. When possible, stock is re-allocated to facilities in the most need or with the least available inventory.

Global best practices. To avoid drug product shortages, global best practices for the anticipatory purchasing of publicly funded vaccines are being explored and adopted.

Temporary compounding & administration procedures. Pharmacists have a number of drug compounding strategies to address temporary shortages, depending on circumstances. For example: using alternative preparations of a drug when other formulations, volume sizes or concentrations are available; repackaging the drug or compound in the required strengths or formulations; and changing the method of administration (e.g., from intravenous to oral).

Usage restrictions. In order to conserve the supply of a drug in shortage, front line RHA facilities may employ usage constraints or rationing policies – restricting the administration of the drug for only those cases where the use of an alternative is not possible or available.

Dedicated resources. Many hospital pharmacies, and some community pharmacies, have devoted staff and resources for the management of drug shortages on a permanent or part-time basis. These individuals may have a number of responsibilities including:

- monitoring ongoing drug shortages and availability of drugs;
- maintaining up to date information on specific vendors and products;
- evaluating impact of shortages on facility;
- consulting clinical teams on appropriate use;
- retrieving stock and redistributing to areas of greatest need;
- implementing prescribing restrictions;
- educating staff on impact of drug shortages;
- facilitating weekly backorder meetings for inventory group;
- distributing regional drug shortage bulletins to stakeholders (e.g., physicians, nurses, pharmacists, administrators, etc.); and
- developing mitigation strategies with key stakeholders to reduce use of at risk drugs.

3.5 Horizontal Drug Shortage Committees

There are a number of horizontal committees and working groups assembled to collaboratively address drug shortages in Canada. At all levels of the supply chain, inter-disciplinary teams actively collaborate to prepare for and react to drug shortages. For example, many hospitals have drug shortage groups comprised of pharmacists, physicians, and nurses to ensure the most efficient and effective responses on the ground.

At a more national level, there are three collaborative groups working to advance drug shortage mitigation, management and communication strategies. Each is briefly described below.

3.5.1 Multi-Stakeholder Working Group

The Multi-Stakeholder Working Group is made up of industry and health professional associations. The Working Group participated in the development and design of ***www.drugshortagescanada.ca***, through consultations led by Health Canada. .

3.5.2 Provincial/Territorial Drug Shortage Task Team

The P/T Drug Shortage Task Team was created by the P/T Deputy Ministers of Health in March 2012 in response to the Sandoz supply disruption. Chaired by Manitoba Health, Seniors and Active Living and comprised of representatives from all P/Ts, RHAs, hospitals , GPOs, and the Task Team communicates broad reaching shortages between jurisdictions and has been useful in identifying, tracking and responding to critical and emerging shortages. The Task Team is shifting focus to a longer-term strategic perspective and greater attention to shortages in community settings.

3.5.3 Multi-Stakeholder Steering Committee on Drug Shortages (MSSC)

As noted in the Foreword, the MSSC was struck in August 2012. The Committee is co-chaired by a representative from one of the P/T Ministries of Health and Health Canada and includes a number of industry and healthcare organizations from manufacturing, distribution and front line delivery. MSSC objectives include drug shortage prevention and mitigation, crisis management and resolution, and building knowledge and sharing information.

Appendix A – List of Contributors

Alberta Health
BIOTECanada
Canada's Agency for Drug and Technologies in Health
Canada's Research Based Pharmaceutical Companies
Canadian Association for Pharmacy Distribution
Canadian Association of Chain Drug Stores
Canadian Generic Pharmaceutical Association
Canadian Pharmacists Association
Canadian Society of Hospital Pharmacists
Capital District Health Authority, NS
Central Health, NFLD
Fraser Health Authority, BC
Health Canada
Health*PRO*
Interior Health Authority, BC
Lower Mainland, Pharmacy Services, BC
Manitoba Health, Seniors and Active Living
MEDBUY
Merck
Northern Health, BC
Pembroke Regional Hospital, ON
Public Health Agency of Canada
Public Works and Government Services Canada
Provincial/Territorial Drug Shortage Task Team
Regina Qu'Appelle Health Region, SK
Rouge Valley Health System, Ajax, ON
Royal Victoria Hospital
Saskatoon Health Region, SK
Sunnybrook Health Sciences Centre, ON
Trillium Health Centre, ON
University Health Network, ON
Vancouver Island Health Authority, BC
Victoria General Site Centennial, NS
Winnipeg Regional Health Authority Logistics, MB

Appendix B – Acronyms and Abbreviations

API – Active Pharmaceutical Ingredients
BCP – Business Continuity Plan
BPP – Federal/Provincial/Territorial Bulk Purchasing Program for Vaccines
CADTH - Canadian Agency for Drugs and Technologies in Health
CDR – Common Drug Review
CGPA - Canadian Generic Pharmaceutical Association
DIN – Drug Identification Number
DND – Department of National Defence
DPD – Drug Product Database
EL – Establishment License
F&DA/R – Food and Drug Act and Regulations
F/P/T – federal/provincial/territorial
GMP – Good Manufacturing Practices
GPOs – Group Purchasing Organisations
HC – Health Canada
IMC - Innovative Medicines Canada
MSSC – Multi-Stakeholder Steering Committee on Drug Shortages
MRAs – Mutual Recognition Agreements
NESS – National Emergency Stockpile System
NOC – Notice of Compliance
OECD – Organisation for Economic Co-operation and Development
PHAC – Public Health Agency of Canada
Protocol – Protocol on the Communication and Notification of Drug Shortages
P/T – provincial/territorial
P/Ts – provinces and territories
PSPC – Public Services and Procurement Canada
RCMP – Royal Canadian Mounted Police
RFP – Request for Proposal
RHAs – Regional Health Authorities
SAP – Special Access Program
Task Team – Provincial/Territorial Task Team on Drug Shortages
Toolkit – Multi-Stakeholder Toolkit
VSWG – Vaccine Supply Working Group
WHO – World Health Organisation
Working Group – Multi-Stakeholder Working Group on Drug Shortages