



National Collaborating Centre  
for Infectious Diseases  
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# **A Call to Action: An Evidence Review on Pharmaceutical Disposal in the Context of Antimicrobial Resistance in Canada**

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## Introduction

Antibiotics are some of the most commonly prescribed pharmaceutical agents in the world, including in Canada. During manufacturing, antibiotics can seep or be discharged into the environment. However, a significant amount can also enter the environment through improper disposal practices (i.e., in sinks, toilets, and household garbage) and natural human excretion. Wastewater treatment systems are not capable of completely removing pharmaceutical residues from entering water supplies and spreading to other environmental features such as soil and surface waters (1–3). There is a range of strategies adopted across the European Union (EU) for collection and disposal of these agents, whilst in Canada approaches are uneven. Where they exist, programs in Canada are estimated to collect only a fraction of unused and expired pharmaceuticals in this country (4).

The accumulation of antibiotics and other antimicrobial agents in the environment can contribute to antimicrobial resistance (AMR), the constant evolutionary modification in viruses, bacteria, fungi, and other pathogens against naturally occurring and synthetic antibiotics, antivirals, and antifungals. AMR is considered to be a serious threat to humans worldwide, as drug-resistant strains of common infections, including tuberculosis and malaria, claim the lives of as many as 700,000 people annually (5). Annual deaths due to AMR are estimated to rise to 10 million annually by 2050, leading to an economic loss in excess of US \$ 100 trillion (5). AMR is responsible for over 25,000 deaths annually across the EU and represents an annual cost of more than € 1.5 billion due to additional healthcare costs and productivity losses (6). In Canada, about 20,000 hospitalized patients develop a drug-resistant infection each year, incurring about \$ 50 million in direct medical costs (7–9). The Ontario Medical Association noted in 2013 that infections are becoming more frequent, deadly, and increasingly more difficult to treat, and that patients are suffering longer with infections that often would have been treated relatively quickly in the previous five to 10 years ago (10). The reported rates of methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections in pediatric hospitals, vancomycin-resistant *Enterococcus* (VRE) bloodstream infections in adult hospitals, as well as drug-resistant *Neisseria gonorrhoeae*, have all increased between 2014 and 2015 (11), and continue to rise (12). One estimate is that that 1 in 16 patients admitted to Canadian hospitals will acquire a multi-drug resistant infection (7).

Antimicrobial overuse (including over-prescribing) and misuse (i.e., under completion or improper adherence to regimens) are common and are considered to be important factors that contribute to AMR (9). A 2014 commentary published in the Canadian Medical Association Journal highlighted a 2005 systematic review that found that more than one-third of patients did not complete their antibiotics course as prescribed, and unused antibiotics (from past infections) were taken by more than one-quarter of patients for new infections (13). Patients with new bacterial infections who use leftover antibiotics can delay medical assessment, while hindering correct diagnoses and the use of a potentially more suitable antibiotic (13).

In 2017, about 24 million antibiotics were prescribed in Canada, mainly in community settings (14). Canada ranked fourth highest among OECD countries for antibiotic prescriptions filled, following France, New Zealand, and Australia in 2015 (15). Not only are antimicrobials prescribed to Canadians for their

own use, but a substantial proportion is also used in veterinary medicine and in agriculture for livestock husbandry. In reports to the 2014 Senate Standing Committee on Social Affairs, Sciences and Technology on Prescription Pharmaceuticals in Canada, witness statements from subject matter experts suggest that as much as 80% of antibiotics are used in animals and livestock (4).

Both excretion of drug residues and run-off into water systems are understood to contribute to the presence of antimicrobials in the environment (Figure 1). Several antimicrobials such as antibiotics, antifungals, and antivirals have been found in water and soil and their presence may play a role in accelerating the development, continuance, and spread of resistant microbes (2,6,16), further reducing the effectiveness of standard first-line antibiotic treatments (16). Almost two decades ago in 2001, the European Commission identified a link between antibiotic waste and the threats of superbugs resulting from antimicrobial resistance (17). The UN Environment report, *Frontiers 2017: Emerging Issues of Environmental Concern from UN Environment*, has presented evidence linking the discharge of drugs or chemicals into the environment to the growing issue of AMR, identifying this as one of the biggest threats globally (18).

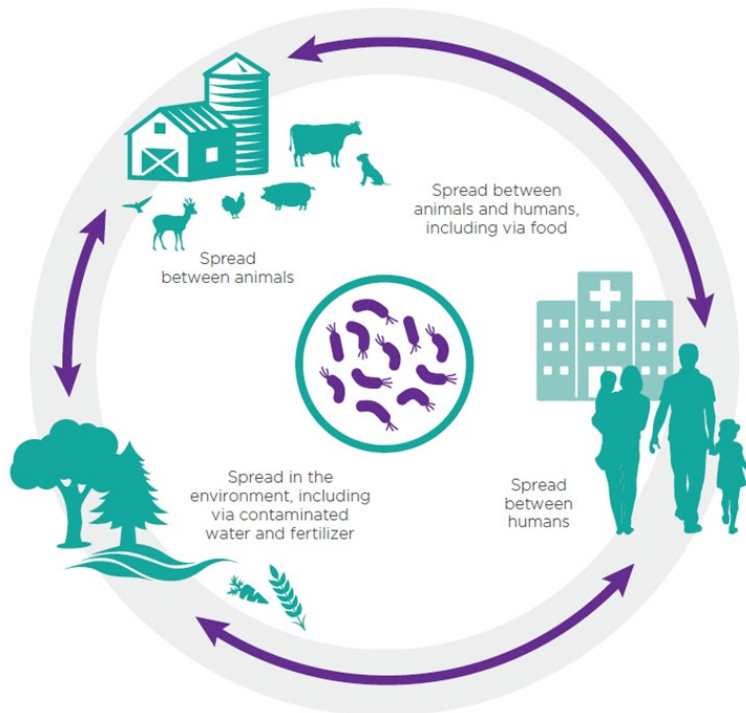


Figure 1. A One Health Perspective of the Connections of Antimicrobial Resistance.  
Source: Government of Canada (9).

The *Pan-Canadian Framework for Action on AMR* (9) and the forthcoming pan-Canadian Action Plan are among the latest steps towards more cohesive approaches to plan for and combat the increasing threat of AMR in Canada. Various discussions and documents call for AMR surveillance programs to integrate, or at least consider, both human and animal health sectors. There is also agreement on the need to work towards a better understanding of the contribution of environmental factors to AMR, and opportunities to mitigate the risk of AMR in the environment (9,19).

For over 10 years, the National Collaborating Centre for Infectious Diseases (NCCID) has contributed to knowledge translation and information exchange on antimicrobial resistance and antimicrobial stewardship (AMS). In partnership with the National Collaborating Centre for Environment Health (NCCEH), NCCID determined to explore existing evidence on antimicrobial disposal systems in Canada as one aspect of the potential threat of AMR in the environment.

To this end, NCCID conducted this review of evidence to describe the current state of knowledge, policies, guidance, and programs for the disposal of pharmaceuticals, with a focus on antimicrobial drugs in Canada. This review situates the problem of improper pharmaceutical disposal practices in the Canadian context by examining the federal, provincial, and territorial guidelines in Canada. Further, the review describes strategies adopted by two OECD countries to identify promising practices for pharmaceutical disposal, for consideration and adaptation in Canada.

The objectives of this evidence review are to:

- Summarize the evidence available regarding the nature and extent of antimicrobial residues in environmental soil and water in Canada.
- Identify and compare regulatory structures, guidelines, and programs for antimicrobial disposal across the country.
- Explore systems and structures outside of Canada, especially in OECD countries, to identify promising practices for pharmaceutical disposal that could be adapted to the Canadian context.

## Methods

The aim of this review is to understand how pharmaceuticals in the environment influence antimicrobial resistance, the scope and nature of pharmaceutical disposal programs in Canada, and to provide examples of such programs that could be adopted for the Canadian context. The review of evidence provides a real-world understanding of the available literature, offering a better contextual framework for needs assessment and gap identification in the subject area. This evidence review aims to capture a deeper understanding of pharmaceutical disposal strategies in Canada with best practice examples from European countries. A three-pronged approach was used to retrieve academic literature published in Canada and internationally as well as from grey literature sources.

Peer-reviewed literature published in Canada was searched using key databases (PubMed, CINAHL, EBSCO-Host, Medline-Ovid, ProQuest, Scopus and Web of Science) through the University of Manitoba online database, with MESH terms related to “pharmaceutical disposal in Canada” and “drug disposal system in Canada” and “disposal mechanism of pharmaceuticals in Canada” identified through a pilot review of the literature. The search was limited to English language records published prior to July 30th, 2019. Searches were repeated in February 2020 to locate any more recent studies.

To provide an international perspective, a search was conducted for key documents published by the World Health Organization (WHO), the European Union (EU), the OECD and the European Union. In addition, an open search with no country limitation was conducted on PubMed, CINAHL/ EBSCOHOST and Medline Ovid with the key search term “pharmaceutical waste disposal”. The search was limited to pharmaceuticals intended for human use in full text published in the last five years (2015-2019). The same search parameters were expanded to ProQuest which included databases for consumer health, environmental science and pollution, psychology, public health, health and medical collections, healthcare administration, Medline, nursing and allied health.

Thirdly, a search for publicly available information was completed to identify newspaper articles, and magazines published in Canada addressing the effects of pharmaceutical disposal, with an emphasis on antimicrobials. Government websites such as Statistics Canada, Health Canada, and Environment Canada were searched to collect the latest statistics, other government reports, and existing guidelines published in Canada. A search was also conducted via the websites of national, provincial and territorial agencies such as NAPRA (National Association of Pharmacy Regulatory Authorities), HPSA (Health Product Stewardship Association), ISMPC (Institute for Safe Medication Practices Canada), CIHI (Canadian Institute for Health Information), CADTH (Canadian Agency for Drugs and Technologies in Health) to find information on mechanisms or guidelines for the pharmaceutical disposal infrastructure within the country. Relevant studies cited in reports and documents were identified and searched individually.

A total of 119 records were retrieved and reviewed in detail, of which 104 documents were deemed relevant for inclusion, comprising full articles, government reports, website information, magazines, federal and provincial websites, national associations and professional organizations.



## Pharmaceutical Metabolites in the Environment

Prescription drug sales in Canada were forecast to be as much as \$34.3 billion in 2019, an increase of 2.7% over the previous year (20). Although not evenly dispersed across the population, this represents an average cost of about \$ 1,074 per capita in 2018 (15). According to one estimate, more than 3,000 compounds are used as pharmaceuticals from 24 different therapeutic classes, with antibiotics being among the most commonly consumed agents (21).

Pharmaceuticals and their metabolites are biologically active substances with metabolic implications, not only for human physiology, but also for other organisms in the environment. According to the UN Environment *Global Environment Outlook 2019*, “pharmaceuticals are commonly mishandled from cradle to grave” (22). In Europe, about 50% of solid medicinal products are unused, whereas in the UK, 20% of individuals surveyed indicated that they disposed of unused medicines in household waste. In Germany, about 23% of unused medicines are discarded by dumping them down drains and an estimated 364 tonnes of active pharmaceutical ingredients are flushed away each year (23).

Over 20 years ago, the annual cost of medication waste in Ontario was estimated to exceed \$40 million Canadian (CAD); when extrapolated for the rest of Canada, the wastage would have surpassed \$110 million at that time (24). A survey conducted in 2002 by Compass Inc. found that Ontario and British Columbia residents were more likely to dispose of unused and expired prescription drugs in household garbage – about 44-46% respondents compared to 32-35% from other provinces. On the other hand, residents from Quebec were more likely to return unused medications to a pharmacy and least likely to dispose them improperly in a sink or toilet (25).

Pharmacologically active substances can enter the environment through several pathways (Figure 2):

- the discharge of effluent from urban wastewater (sewage) treatment plants containing both excreted and unused pharmaceuticals discarded in sinks and toilets;
- animal manure and aquaculture (dispensed with animal feed);
- discharge of effluent from manufacturing plants;
- spreading of sewage sludge, grazing livestock, veterinary treatment of pets; and
- improper disposal of unused pharmaceuticals and contaminated waste into landfills.

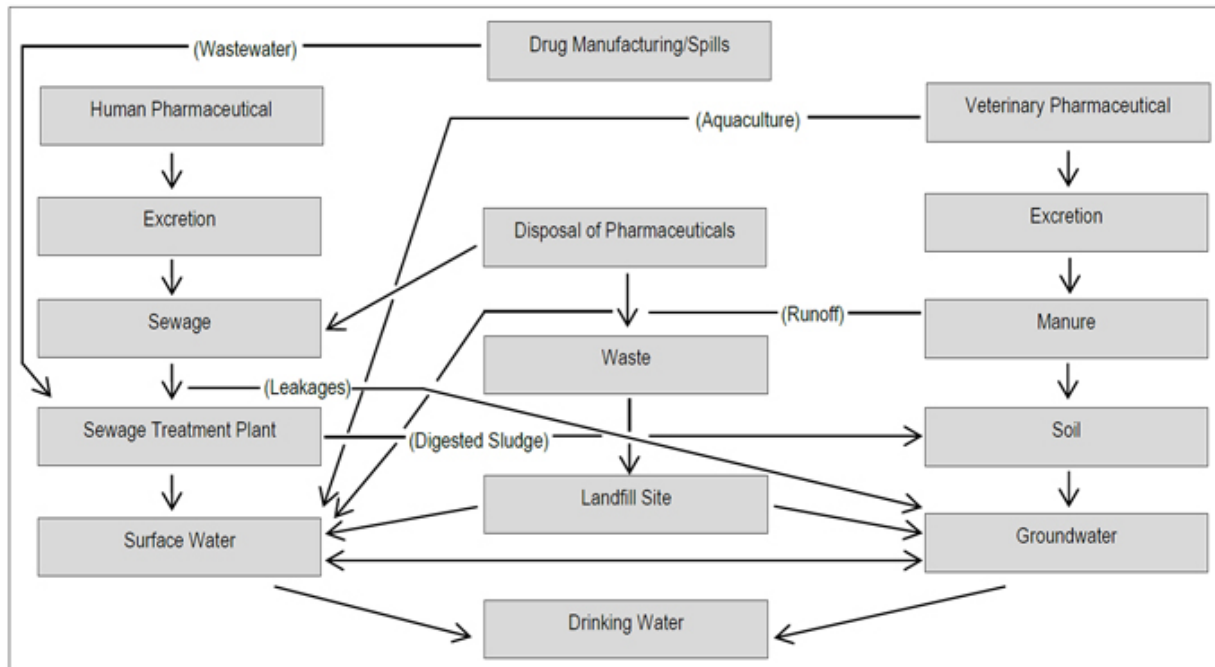


Figure 2. Sources and Pathways of Pharmacologically Active Substances into the Environment (Adapted from World Health Organization (3).

In the case of commonly used antibiotics, BIO Intelligence notes that about 80-90% of the Amoxicillin consumed by humans passes through the body un-metabolized and can enter into sewage directly, while, 45-62% of Ciprofloxacin, another common antibiotic, consumed is excreted in its original form urine and 15-25% is excreted in feces (23).

A study from Ontario, published in the Water Quality Research Journal of Canada, found traces of pharmaceuticals in drinking water in 15 southern Ontario cities, including ibuprofen, cholesterol-lowering drugs, and triclosan (an antimicrobial agent commonly used in toothpaste, soap, and dish detergent) (26). In analyses of three septic system plumes in Ontario in 2008, triclosan and a number of pharmaceuticals were found in groundwater as the result of septic system wastewater seeping into the subsurface (27).

## Effects of Pharmaceutical Contaminants on Aquatic Life

A 2013 European study found that several veterinary drugs, mostly antibiotics, contaminated the majority of the 29 small waterways analyzed across 10 EU countries (6). The study found that pharmaceutically active substances and their metabolites at all stages of their cycle can remain in drinking water even after water treatment and processing. These compounds may also leach into natural water systems, where they can accumulate in fish, vegetables, and livestock. The effects of these substances on aquatic organisms and other animals have been well established in the scientific literature (28). For example, a 2011 study conducted in Canada found six antidepressants concentrated in the liver and brain of freshwater fish exposed to municipal wastewater effluents (29). Another Canadian study conducted near Kenora, Ontario found that exposure to synthetic estrogen interfered

with the ability of fathead minnows to reproduce which consequently resulted in a decline in the size of the lake trout population and disrupted the natural balance of the ecosystem (30). Numerous other studies have provided supporting evidence for the dangers associated with pharmaceuticals such as 17  $\alpha$  ethinyloestradiol and some antibiotics leaching into the environment, and the detrimental effects on invertebrate species (30–32).

Although only trace amounts of pharmaceutical agents have been detected in water, there is a growing concern that drugs may have a cumulative effect on microorganisms that are in contact with the contaminated water. Currently, limited knowledge is available on the potential mechanisms through which pharmacologically active chemicals interact with the ecosystem to select for antibiotic resistance (39). A Saskatchewan study in Wascana Creek (Regina) reported the presence of seven pharmaceuticals and personal care products (PPCPs) including antibiotics such as erythromycin, trimethoprim, sulfamethoxazole and triclosan in high concentrations, posing a threat to aquatic life (32). Data from unpublished research by Waiser and Lawrence, demonstrates that a concentration of erythromycin as low as 1 $\mu$ g/L water was not only harmful for aquatic bacterial production but also changed the composition and structure of attached microbial biofilm communities in the same lake (as cited by (32)). Erythromycin and other macrolide antibiotics are known to disrupt the transcription and/or translation process in the photosynthetic chloroplast and inhibit protein synthesis of cyanobacteria and green algae phylogeny (32). The same study found that Trimethoprim may also pose a risk to aquatic plants in the Wascana Creek by interfering with the synthesis of folate, a vitamin needed for photorespiration. Similarly, the reported concentration of sulfamethoxazole found in the water could affect phytoplankton in the creek, while sulfonamide, a bacteriostatic antibiotic, could limit metabolic pathways in both bacteria and in plants (32).

In contrast, the direct effects of pharmaceuticals in the environment on human health appear to be less well studied. Expert opinions suggest that there may be non-targeted, unintended effects at sub-therapeutic doses due to exposure to the chemicals (33). Long-term exposure to combinations of different pharmaceutically active substances, especially on vulnerable populations, is under WHO observation (34). Sauvé found that after drinking two litres of water every day for 70 years, the body would only accumulate about 1% of the normal daily dose of someone intentionally taking that medication (35). According to a letter to the European Council, even the best, most expensive, and highly sophisticated wastewater treatment is not able to remove 100% of all pharmaceutical residue (28). In fact, it has been noted that these expensive and sophisticated technologies can create additional by-products that are rarely measured when assessing the potential of these treatment processes. One example is the ozonation of the anticonvulsant drug carbamazepine, which can yield three new active compounds. Similarly, chlorine, a commonly used disinfectant in water, reacts with naturally occurring organic matter found in water. Other examples include estrogenic steroids used in contraceptives, anti-inflammatory agents such as ibuprofen, and triclosan which can react with ultraviolet filters (36). These findings, or the lack thereof, highlight the urgency and need for more research to investigate the direct long-term human health effects of unintentionally consuming pharmaceuticals from drinking water, as well as the indirect effects of pharmaceutical environmental pollution.

## Antibiotics in the Environment

According to the Public Health Agency of Canada's report on the Canadian Antimicrobial Resistance Surveillance System (CARSS), in 2016 about 92% of the total antimicrobials prescribed for human use were dispensed in the community and the remaining 8% was used in hospitals. In the same year about 1.0 million kg of antibiotics were distributed for use in animals, of which 99% were used in food-producing animals and 1% for companion animals (11).

According to the information website, *I Don't Flush*, 25% of Canadian households have unwanted or expired medications stored at home (37). Health Canada found that close to 40% of Canadian households disposed of their unused or expired medications down a drain or toilet, or putting them in curbside garbage (1).

Over a 16-month period from September 2005 to December 2006, the Ontario Ministry of Environment conducted analyses of samples from 17 different water systems (rivers, lakes and groundwater) as part of the Ministry's Drinking Water Surveillance Program (DWSP). The survey found 25 antibiotic compounds in water samples; of these, 14 were detected in untreated water sources and about 12 were detected in finished drinking water. Compounds enter these natural water systems through household consumption, agricultural consumption, or through the discharge of sewage water treatment plants to the surface water.

## Effects on Rural and Vulnerable Populations

Environmental exposure to antibiotics is not only seen in urban waterways, but has also been observed in rural and on-reserve communities. A 2014 study conducted on water quality on 17 First Nations communities in Ontario indicated that widely used pharmaceutical agents in humans, veterinary drugs, and aquaculture, such as analgesics, anticonvulsants, antibiotics, antihypertensive, antacids, and contraceptives were detected in water streams of four different ecozones or "cultural areas": the Boreal Shield / Subarctic (Alberta), Boreal Forest Northeast (Newfoundland), Hudson Plains (Northeastern Manitoba across Ontario into Western Quebec), Mixed-wood Plains (Southern Ontario, Great Lake region Huron, Erie, Ontario extending to St. Lawrence River to Quebec City) (39). The study found that measurable quantities of antibiotics such as Ciprofloxacin, Clarithromycin, Erythromycin, Sulfamethazine, Sulfamethoxazole and Trimethoprim were detected in both wastewater and surface waters (39).

Another important concern is the exposure to trace amounts of pharmaceutically active substances to vulnerable populations, such as immunocompromised patients, seniors, pregnant women, and infants who drink formula mixed with tap water (35). In 2011 Health Canada expressed concern about the long-term exposure to trace amounts of these agents in these vulnerable populations and the potential rise in drug-resistant infections (40).



# Pharmaceutical Disposal in Canada

## Legal Framework in Canada

In Canada, preventing and managing AMR is a responsibility shared among many stakeholders, involving all levels of government, public, and private organizations. One Health is a multidisciplinary approach that integrates human, animal, and environmental perspectives to address the evolving threat of AMR, as well as other public health issues.

In 1992, the Canadian Council of Ministers of the Environment developed the national standard guidelines for the management of biomedical waste in the environment to streamline the different waste management and disposal practices among provinces and territories. These guidelines were aimed to build uniformity in mechanisms and regulations for disposal practices in the Canadian healthcare system (41). The Canadian Environmental Protection Act (CEPA) of 1999 is the principal federal law that safeguards the environment and human health and is mutually regulated by Environment Canada and Health Canada (42,43). This act provides federal legislation for numerous environmental and health protection programs which includes the assessment and management of risks from chemicals, polymers, living organisms, hazardous waste, ocean disposal, and environmental emergencies due to air and water pollution (44).

## Federal Guidance

Under CEPA 1999, Environment and Natural Resources Canada has developed the New Substances Program which administers the New Substances Notification Regulations (Chemical and Polymers) and the New Substances Notification Regulations (organisms) (NSNR) (45). According to these regulations, substances that are entering or may enter the country in a quantity of more than 1000 kg per year must be reported with the identity, and experimental data and exposure information of the given substances to Health Canada or Environment and Climate Change Canada (ECCC). Environmental risk assessment of pharmaceuticals is a joint responsibility of Health Canada and ECCC. Before manufacturing or importation of any new substances into Canada, a clearance report must be submitted to these government departments to assess for any potential adverse environmental effects or anticipated adverse effects associated with the substances (43). The Domestic Substances List (DSL) includes non-toxic substances that have no environmental repercussions and hence they are permitted to be imported into and manufactured in Canada under the CEPA Section 81 sub-section (1, 3).

The 2018 annual report by ECCC on CEPA 1999 is the latest document discussing research conducted on the occurrence, fate, and eco-toxicity of specific pharmaceuticals in Canadian wastewater treatment systems, along with the development of analytical methods for the identification of degraded pharmaceuticals in surface waters (46). The Chemicals Management Plan (CMP) is a collaborative effort between Environment Canada and Health Canada with the goal of addressing environmental concerns including the disposal of pharmaceuticals (4). This plan aims to develop a scientific evaluation framework to assess the potential harms to humans and the environment from the common use and

disposal of chemicals, along with the development of risk management strategies and conducting more research (9).

Health Canada's Directorate of Controlled Substances has guidance documents for pharmacists, practitioners, and persons in charge of hospitals regarding the handling and destruction of unserviceable stock containing narcotics, controlled drugs, or targeted substances. The guidance document also includes instructions for the handling and destruction of post-consumer returns containing controlled substances (CS-GD-021) (47,48). In 2019, Health Canada released recommendations in the areas of security, inventory reconciliation, and record-keeping for community pharmacists, with a section on post-consumer returns and appropriate mechanisms of disposal by pharmacy staff. As of April 2018, Health Canada no longer requires pharmacists to record the name, strength, and quantity of drugs for post-consumer returns, allowing pharmacists to treat controlled and uncontrolled substances equally and to make safe disposal of all substances easier, though each province may have its own regulations in place for specific controlled prescribed medications (e.g., fentanyl) (49).

## **Pharmaceutical Surveillance Guidelines for Water**

In the international context, there is no legally binding regulation or any guidance on how pharmaceutical companies should dispose of their waste in an acceptable and environmentally-safe manner. The decision is left up to individual companies to create internal policies for the handling and disposal of pharmaceutical waste at the manufacturing level, contributing to a lack of transparency and the observed lack of standardization (50). According to Health Canada, the absence of a national systematic mechanism makes it challenging to monitor prescriptions written and consumed due to the fragmented system. This creates difficulties in estimating the effectiveness and cost spending patterns of consumers in Canada (51). There is no formal environmental surveillance to track the presence of pharmaceutical contaminants in freshwater systems and other water sources across Canada (4). Environment Canada's Pharmaceuticals and Personal Care Products Surveillance Network has an informal program which is responsible for systematic sampling and testing. Public reporting on these environmental contaminants conducted by independent scientists and researchers is left up to individual companies, and as a result, their findings are normally only documented in peer-reviewed journals (4). A recent technical study from the ECCC found that the work on pharmaceutical discharge into Canadian lakes is disjointed and there are no mandatory monitoring procedures or emission limits imposed on pharmaceutical disposal into lakes (52). Overall, federal and provincial legislation, regulations, and policies including treaties for the Great Lakes environment do not provide any directives for pharmaceutical discharge into the Great Lakes or any other water systems across Canada. However, according to pharmacopeia standards, pharmaceutical manufacturers are required to remove all pharmaceutically active substances and their metabolites from their wastewater (53).

In Canada, there are currently no drinking water quality guidelines for acceptable concentrations of pharmaceuticals except for 17  $\alpha$ -ethinylestradiol, which is set at 0.5 ng/L in British Columbia and there is limited information in the literature for quality guidelines (39,54). In contrast, Australia has set a drinking water guideline for water recycling of 1.5ng/L of pharmaceuticals in drinking water (39).

Through the federal regulation on Water Systems Effluent Regulation (WSER), the effluent from the sewage treatment plants (STPs) is discharged to receiving bodies. However, this regulation is conventionally limited to measure metals, nutrients, oxygen demand and some organics (55), resulting in wastewater treatment plants being one of the sources for pharmaceutical contamination (9).

## Provincial Guidelines for Disposing Pharmaceuticals

In the provinces and territories, there is a mixture of guidelines and regulations for the appropriate disposal of pharmaceuticals. Table 1 offers a summary of requirements to dispose of pharmaceutical agents and any existing regulatory framework in each jurisdiction.

Alberta, Saskatchewan, and Nova Scotia have voluntary programs, administered and monitored by their respective pharmacy associations. British Columbia, Manitoba, Prince Edward Island, and Ontario all have regulated programs for the disposal of pharmaceutical waste (14, 15, 16). On May 11, 2013, the first national prescription drug drop-off day was organized by Public Safety Canada, in coordination with the Canadian Association of Chiefs of Police, which collected more than two tonnes of unused medications from consumer returns (13). The following are the specific programs in each jurisdiction.

**British Columbia** - The *British Columbia Environmental Management Act* recycling regulation applies to pharmaceutical disposal in the province and highlights the extended producer responsibility plans (56). *The Recycling Regulation of the Environmental Management Act* (B.C. Reg. 449/2004) is the Act that outlines the process for pharmaceutical disposal (18).

**Alberta** - Alberta Health Services has issued a Waste Management policy for biomedical waste (ESM-01-01), including pharmaceuticals (57). The City of Calgary provides a web link that redirects to the Alberta Pharmacist Association (RxA) to inform the residential disposal strategy for the return of unused or expired medications (19). The Health Quality Council of Alberta has also designed a medication management checklist for supportive living which also includes elements of medication disposal and return strategy (58).

**Saskatchewan** - The Saskatchewan College of Pharmacy Professionals created guidelines on pharmaceutical waste disposal services in the province as a reference manual based on the Government of Saskatchewan's *Biomedical Waste Management Guidelines* of February 2008 for proper disposal of biomedical waste products (59,60). The Saskatchewan College of Pharmacy Professionals provides tips for proper disposal of medication for the public as well (61).

**Manitoba** - Manitoba Health has outlined a policy and procedural document for returning publicly funded vaccines and biologics to the Provincial Vaccine Warehouse (PVW) for cost recovery. Products which are not returned to PVW, should be disposed of in an appropriate biologics container (62)<sup>1</sup>.

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<sup>1</sup> We note that there are not specifications provided for the "appropriate biologics container".



The Winnipeg Regional Health Authority (WRHA) has primary health care operating guideline on medication storage, restocking, disposal & return process for non-narcotics and targeted/controlled substances, which also includes a logbook of all, returned, expired and discarded supplies (63). In 2019, the WRHA infection prevention and control program issued an operational directive as part of an infection prevention and control manual, providing clear guidance on the disposal of pharmaceutical waste (64). Less information is available for consumers to dispose of their unused pharmaceuticals properly.

**Ontario** - According to Ontario Regulation 298/12 made under the *Environmental Protection Act*, pharmaceuticals including sharps/syringes are the responsibility of local pharmacies for safe disposal provided free of cost to the consumer. The Ontario Medication Return Program (OMRP) is a stewardship program offering safe and easy disposal for Ontarians (65).

Guideline C-4 deals with the management of biomedical waste in Ontario and is categorized into different classes. The province has taken a “source-to-tap” approach to test source water for pharmaceuticals and personal care products (PPCPs) and has found contaminants in the past. They continue to study the effectiveness of water treatment technologies to reduce pharmaceuticals and other contaminants (35). Through Environmental Compliance Approvals (ECAs), Ontario regulates the effluent limits from sewage treatment plants (STPs) to receiving bodies (55). Organic and inorganic chemical manufacturing industrial wastewater in Ontario is regulated by the *Ontario Water Resources Act*, which outlines site-specific effluent limits in addition to monitoring and reporting requirements (9).

**Quebec** - The Environment Quality Act deals with the regulation of hazardous materials and further categorizes hazardous materials into sub-groups (66).

**Newfoundland & Labrador** - The Department of Environment and Climate Change Pollution Prevention Division in Newfoundland & Labrador has issued a guidance document on the management of biomedical and pharmaceutical waste, including clear guidelines on storage and disposal methods for various pharmaceutical waste in the province (67).

**Nova Scotia** - The Pharmacy Association of Nova Scotia (PANS) has administered the medication disposal program at no cost for the public to return any unneeded medications to their local community pharmacies (“Medication Disposal | Pharmacy Association of Nova Scotia,” 2019).

**Prince Edward Island** - PEI environmental protection act-material stewardship and recycling **regulations** have a clause on the pharmaceutical product stewardship program (Section 89) for proper disposal of pharmaceutical products (69).

Table 1. Provincial and Territorial Guidelines for Disposing of Pharmaceuticals.

Provincial/Territorial Program (Year Established)	Funding	Regulated	Nature of Participation	Collector & Disposal
Alberta ENVIRx program	Drug manufacturers	Not regulated	Voluntary participation by consumers & community pharmacies -- Alberta Pharmacists Association	G-M Parson
British Columbia (ENVIRx program – (1999))	Drug manufacturers	Regulated under Environment Management Act (EMA), specifically under Recycling Regulation	Voluntary participation British Columbia Medications Return Program Health Products Stewardship Association	Phase separation solutions
Manitoba – formal program - 2011	Drug manufacturers	Regulated under The Waste Reduction & Prevention Act	Voluntary participation for consumers, however a regulation process is underway for producers & distributors: Manitoba Medications Return Program Health Products Stewardship Association	Stericycle
New Brunswick---no formal province-wide program (Household hazard waste 1998)		Solid waste commission— regulated by the Regional Solid Waste Commissions Regulation under the Clean Env. Act.	Voluntary participation for public	
Newfoundland and Labrador formal program (Medication Disposal Program mid-1990s)	Government	Not regulated	Voluntary for households & municipalities	
Northwest Territories	No Program in place			
Nova Scotia---formal province-wide program (Medication Disposal Program mid-1990s)	Manufacturers	Not regulated	Voluntary for consumers & community pharmacies— Medication Disposal Program- Pharmacy Association of Nova Scotia	PANS & McKesson
Nunavut	No program in place----do not have territorial program---- do provide collection opportunities			
Ontario—Ontario Medication Return Program 2013	Manufacturers	Regulated under environmental protection act	Voluntary for households & funding will be required by regulation of pharmaceuticals—Ontario Medications Return Program-Health Products Stewardship Association	

Continued...

Prince Edward Island—formal province-wide program (Take it back 2004)		Regulated	Voluntary participation for households and community pharmacies—Island Medications Return Program-Health Products Stewardship Association	Atlantic Industrial Services under contract with IWMC
Quebec---no formal province-wide program			Pharmaceutical Collection—Health Products Stewardship Association	RECYC-QUEBEC—advises Quebec residents about safe pharmaceutical disposal
Saskatchewan—formal province wide program (Pharmaceutical waste disposal 1997)	Pharmacies pay for the program	Not regulated	Voluntary participating for consumers, community pharmacies & the pharmaceutical industry—Pharmaceutical Waste Disposal Program-Pharmacy Association of Saskatchewan	BioMed
Yukon Territory	No formal program—most community pharmacies have informal take-back programs—pharmaceutical waste is collected then shipped to incinerator operated by the Whitehorse General Hospital---territory does provide collection opportunities for consumers			

## Professionals’ Responsibilities

### Pharmacists’ Roles and Responsibilities

As medication providers and dispensers, pharmacists are responsible for patient counselling, compliance, monitoring drug interactions, and ensuring that unused pharmaceutical stock in the pharmacy, as well as unused medications returned by the public, are disposed of appropriately (70). According to the professional code of ethics in Alberta, pharmacists are required to act as environmental stewards by providing safe disposal of both prescription and non-prescription drugs, while also supporting other pharmacy related environmental initiatives (71). Similarly, in Nova Scotia pharmacies are mandated to ensure the disposal of pharmaceuticals is in compliance with environmental guidelines (71). On the same note, the Saskatchewan College of Pharmacists has established its guidelines for pharmaceutical waste disposal regarding licensed disposal services and collection process. The Ontario College of pharmacists guidelines for compounding preparations and the standards for pharmacists for licensed long-term care facilities also recommends that pharmacists follow the environmental requirements for disposal and destruction of drugs (71). The Ontario College of Pharmacists regulation 347 schedules 2(A) and (B) indicates that hazardous waste should be disposed of by a facility that has been licensed to incinerate them (72).

### Hospitals

Hospitals generate large amounts of wastewater containing pharmacologically active substances such as anti-inflammatory drugs, cardiovascular medications (e.g.,  $\beta$ -blockers), antineoplastic drugs, and antibiotics, along with wastewater generated through kitchens, internal laundry, laboratories, toilets, and sinks. The mixed wastewaters are usually discharged directly without pretreatment to sewers for conveyance to treatment systems before being discharged into receiving waters (73).

The Canadian Society of Hospital Pharmacists published the “Controlled drugs and substances in hospitals and healthcare facilities: Guidelines on secure management and diversion prevention” which outlines the process for waste and disposal of unusable drugs in hospitals and healthcare settings. It offers helpful information for pharmacists regarding local destruction in different setting such as in operating theatres, delivery rooms, and other hospital locations where anesthesia and controlled drugs are used (74).

In Canada, there are no provincial and federal regulations regarding medicinal residues in hospital sewage water and no pretest requirement exists for this water (53). The Canadian Council of Ministers of the Environment recommends that landfills should only accept waste that has been decontaminated by the facilities (1). According to the Environment Protection Act, regulation 347 biomedical waste generated by hospitals, veterinary facilities, and other health care services must be treated. In cases where this is challenging, an alternative destruction mechanism must be employed as hazardous waste needs to be treated prior to its disposal in order to reduce potential environmental toxicity (9). As regulated in Ontario, hazardous medical waste must be sterilized prior to disposal at a landfill (75). A 2016 study analyzing final effluent from two hospitals and a long-term care facility in Canada reported the presence of 14 steroids and hormonal compounds, along with 88 other drugs including triclosan compounds (73). Ciprofloxacin was detected in higher concentrations than ofloxacin, consistent with findings from French, Norwegian, and Italian hospital studies. The macrolide class of antibiotics (e.g., azithromycin, clarithromycin, and erythromycin) were also detected in the final effluents. Sulfamethoxazole is another type of antibiotic that was also detected in effluents (73). In Canada, there is a lack of hospital data on the volumes and toxicity of pharmaceutically active substances discharged from hospitals and health care institutions (52). Currently, no regulations exist in Canada at either the federal or provincial level on medicinal residues and pre-treatment of hospital sewage water. It is the responsibility of individual municipalities to pass by-laws to ensure quality and quantity standards which must then be followed by local wastewater treatment plants (9).

## **Dental Clinics**

Dentists in the community are major prescribers of antibiotics. The Colleges of Registered Dental Hygienists from Alberta and Ontario provide guidance on disposal mechanisms for dentists’ offices in these province (76,77). In those two provinces, it is a dentist’s responsibility to ensure proper storage and disposal of expired or unused medications and also safe return of these medications to participating take back pharmacies (78,79).

## **Non-Governmental Pharmaceutical Disposal Systems and Guidance in Canada**

In our review of websites and publicly available documents, we found several organizations that are directly or indirectly involved in disposal strategies at various levels. These include national and local pharmacy regulatory associations, as well as health products and pharmaceutical stewardship associations.

## **Health Products Stewardship Association (HPSA)**

The HPSA is a not-for-profit industry stewardship organization established in 1999 that operates a no-fee medication and other health products return program to manage the safe disposal of those products. THE HPSA was formed by producers of consumer health products in Canada and operates collection and disposal programs that focus on prescription drugs, natural health products, over-the-counter (OTC) medications, and medical sharps waste generated by the public. It was formed to fulfill the producer stewardship obligations in provinces to meet regulations that require them to ensure safe and effective collection of unwanted medications and sharps. The HPSA is mandated to develop program plans and annual reports covering program performance and any additional obligations outlined by the province. Currently, British Columbia, Manitoba, Ontario and Prince Edward Island (PEI) are the four provinces where HPSA manages the medications return programs.

## **Institute for Safe Medication Practices Canada (ISMPC)**

ISMPC is a not-for-profit organization devoted to the advancement of medication safety in all healthcare settings, working collaboratively with the healthcare community, regulatory agencies, and policy makers. The ISMPC also engages provincial, national, and international patient safety organizations, the pharmaceutical industry, and the public to promote safe medication practices. Some of its mandates include analyzing medication incidents, providing recommendations for the prevention of harmful medication incidents, and facilitating quality improvement initiatives. ISMPC does not directly operate any medication return programs, however, they provide information for safe disposal and medication return programs operated under the Health Products Stewardship Association (HPSA) (80).

## **Optimal Medications Return Program Based on Extended Producer Responsibility (EPR)**

Across the world, pharmaceutical producers shoulder considerable responsibility for medication return and disposal programs, whether it is through organizing the collection of pharmaceutical waste from the public or the incineration of the waste. These pharmaceutical manufacturers and distributors are at least fiscally responsible for safely disposing of these agents in many OECD countries free of charge to the consumer. Similarly, in Canada, several jurisdictions have adopted EPR programs, including medication return programs operated in BC and Ontario (15).

## **National Association of Pharmacy Regulatory Authorities (NAPRA)**

The National Association of Pharmacy Regulatory Authorities created a reference document, *Model Standard of Practice for Canadian Pharmacists* for pharmacy operators on the disposal of dispensed drugs and the benefits of responsible environmental practice. It highlights the pharmacist's role in establishing a disposal process in consultation with the relevant stakeholder associations, manufacturers, and other community pharmacists, encouraging public involvement in medication return programs, collecting expired and unused medications, and documenting the volume of pharmaceutical waste collected for proper disposal (81).

The NAPRA embraced medication return programs nationally for a number of reasons, which include consumer and child safety concerns from accidental poisonings, unwitting consumptions of expired medications, or medication exchange. Reduced medication costs, improved therapeutic outcomes and lowering environmental contamination by these pharmaceutically active substances are also issues which medication return programs seek to address (82).

## **Green Healthcare**

The Canadian Coalition for Green Health Care is a not-for-profit cooperation of Canadian health service organizations, associations, and environmentally focused businesses that promotes the adoption of sustainable and environmentally friendly health care service delivery. They initiated a healthcare standard and recognition method as The Green Hospital Scorecard (GHS). This scorecard measures a hospital environmental performance in five areas: Energy, Water, Waste, Pollution Prevention, and Corporate Leadership. It is important to note that the GHS does not target other healthcare facilities, such as dental or primary care clinics (52).

## **Canadian Agency for Drugs and Technologies in Health (CADTH)**

CADTH generated a rapid response report by looking for evidence-based guidelines regarding best practices for unused medication disposal programs. This report was able to find only one evidence-based guideline on best practices for unused medication disposal programs published by the National Institute of Health and Care Excellence in the United Kingdom (83).

## **Corporate Social Responsibility**

There are examples of manufacturers taking a lead in appropriate disposal as part of the corporate social responsibility programs. Sanofi Pharmaceutical, for example, generated a hand out in 2017 providing recommendations for users, *Disposal of Unused Medicines & User Recommendations* (84). This document provides a snapshot of disposal initiatives in France, Czech Republic, Spain, Colombia, Japan, Mexico, and Canada.

The code of marketing from pharmaceuticals states, “companies are responsible for making sure that all excess and/or expired clinical evaluation packages of their own manufacture are returned to the company’s storehouse or head office” (85).

## International Context – What is Happening Around the World?

Around the world, many countries have instituted medication return programs – also called collection programs, take-back schemes, or the disposal programs – which allow consumers to return their unused pharmaceuticals to a pharmacy or collection depot for safe treatment and disposal. The United Nations recommended that countries develop comprehensive waste-management strategies that outline responsibilities and duties of stakeholders in the waste-management process and the national authority responsible for overseeing the implementation of the law and its enforcement (86). It also mentioned that non-governmental organizations (NGOs) in public health should advocate for environmental protection by conducting programs and activities. Strict occupational health and safety standards in hospitals and other health care facilities should be adopted including proper training of staff (86) .

Table 2. Formal Pharmaceutical Return Programs in OECD countries

Country	National Medication Return Program	Funding	Disposal & Pick Up Sites
Sweden	Apoteket AB	Government	Pharmacies
Portugal	Sistema Integrado de Gestão de Resíduos de Embalagens e Medicamentos [Integrated Packaging and Medicines Waste Management System] (SIGREM) operated by Valormed	Pharmaceutical Industry	[Community Pharmacies]
France	Cyclamed	Pharmaceutical Industry (tax of €0.0022 per pharmaceutical drug package on the market to fund Cyclamed)	Pharmacies
Hungary	Recyclomed Kft (Decree no. 11/2017 (VI. 12) addresses waste management activities related to pharmaceutical waste generated from dispensing medications to patients/consumers)	Pharmaceutical Industry -pharmaceutical manufacturer & distributor obligated to set up waste management infrastructure	Pharmacies -collect both human and veterinary medicines
Australia	Return Unwanted Medicines (RUM) project ran by the National Return & Disposal of Unwanted Medicines Limited organization	Mixed: Federal government & Pharmaceutical wholesalers financially support the collection and transportation of waste	Pharmacies
New Zealand	Disposal of Unwanted Medicines Properly (D.U.M.P) Project	Unclear if the DUMP pilot was scaled up - the 3Ts helped to fund the pilot project in the South Western Area Health Board of New Zealand	Pharmacies

Continued...

U.S.A	None (state government responsibility) DEA -recommends that certain medications be flushed down the toilet		Police departments, law enforcement offices -pharmacies were recently allowed to collect following the enactment of the Secure and Responsible Drug Disposal Act - different criteria for controlled substances?
Canada	None: the Canadian constitution delegates waste management to the provinces rather than the federal government -provinces assign responsibility to municipalities, resulting in a process that often involves many different stakeholders - federal involved with waste to some extent		Pharmacies

The EU legislation (Directives 2004/27/EC and 2001/182/EC) deals with the collection of unused and expired human and veterinary medications. It mandates that the medication package specify the precautions relating to the disposal of unused medicinal products and its movement to the appropriate collection system (52).

Since 1999 the European Antimicrobial Resistance Surveillance Network has been collecting data from each member country. Sweden and Denmark were some of the first to take action against the non-medical use of antibiotics in food-producing animals, with the implementation of a cross-sectoral surveillance system, which brought a policy shift leading to the withdrawal of antibiotics as growth promoters. A number of multi-year initiatives were initiated by the European Commission under the EU's Research Framework Programmes on pharmaceuticals in the aquatic environment. These include the Knappe project (2007 – 2008) studying the evidence on pharmaceutical in the aquatic environment; the CYTOTREAT project (2011 – 2014) examining the fate and effects of cytostatic pharmaceuticals in freshwater organisms and in vitro cells and; and the PHARMAS project (2011 – 2014) investigating the environmental and health risk of antibiotics and anticancer drugs in the environment (52).

Among EU member states, Switzerland took the lead to address the issue of pharmaceuticals being detectable in water. Since 2016, the Swiss government introduced a legislation that mandated the conventional wastewater treatment plants to implement an additional process which removes micro-pollutants<sup>2</sup> (52).

Health Canada's 2009 *Pharmaceutical Disposal Programs for the Public: A Canadian Perspective*, published as part of the Environmental Impact Initiative, noted that further research was needed to

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<sup>2</sup> Due to chemical degradation of these active and non-active pharmacological agents, they convert into metabolites which are considered micro-pollutant just like the concept of micro-plastic



identify the proportion of the general public who are aware of and regularly use these formal medication disposal systems, in addition to the amount and types of pharmaceutical waste collected (1). This information will serve as important surveillance for environmental agencies so that pharmaceuticals in the environment can be monitored to anticipate emerging threats to public health. The following comparison of two European systems seeks to examine critical components in the chain of pharmaceutical waste collection and disposal systems that can support antimicrobial stewardship and improve environmental health. The lack of standardization from program-to-program makes it difficult to uniformly evaluate the processes within and between countries and to this end, we primarily focus on two countries as exemplars - France and Sweden.

## **France and Sweden: Two Examples of Pharmaceutical Waste Management in Europe**

### **France**

**Cyclamed** is a non-profit eco-organization responsible for operating the national medication take-back program in France. It was established in 1993 to handle the collection, processing, treatment, and disposal of unused medicinal drugs (UMD) from consumers (87). There are many stakeholders involved from the pharmaceutical industry such as retail pharmacies, wholesalers, and pharmaceutical companies (87).

### **Process**

Consumers are responsible for returning their unused or expired medications to any pharmacy for safe disposal. Wherever possible, consumers are required to separate and empty medications from packaging, discarding the latter in regular household waste bins or recycling containers. Currently, only medications intended for human consumption from households are eligible to be disposed directly through Cyclamed (87). Pharmaceutical waste from other health facilities such as hospitals, dental offices, or veterinary clinics must be disposed through other designated channels (87). Cyclamed collaborates with other organizations to create instructional pamphlets which use pictograms (Appendix A) to demonstrate the steps consumers must take to return unused medicines to their pharmacy (87). As the main collection sites, pharmacies can request unused medication collection cartons from the appropriate Cyclamed partners. This specific carton is designated solely to collect pharmaceutical waste, separate from other biohazard or infectious waste. These cartons are then transported to Cyclamed's energy recovery units and a waste tracking slip is generated to monitor the amount of unused pharmaceutical waste that has been incinerated (87). Cyclamed's Operating Principle and processes are illustrated in Figure 3.

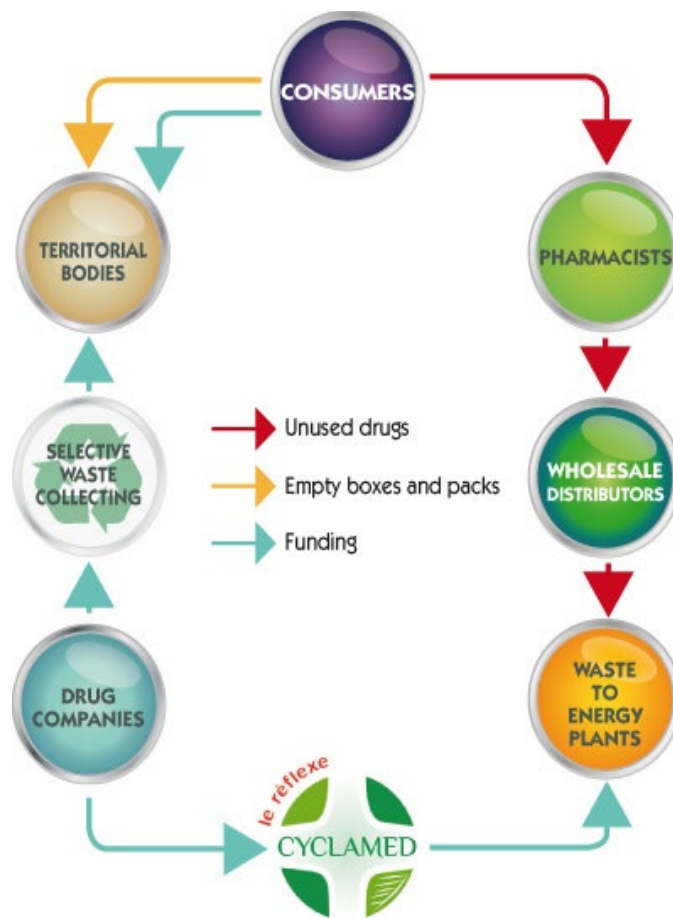


Figure 3. Cyclamed’s Operating Principle and Flow of Pharmaceutical Waste (from (87)).

## Regulations

In addition to *Directive 2004/27/EC of the European Parliament and the Council of European Union*, which instructs countries in the European Union to implement the necessary infrastructure to collect and dispose of unused medicinal drugs (88), France has enacted legislation to further enforce this directive. Cyclamed’s mission is “to collect medicines safely in order to preserve the environment and public health” and as of February 27, 2007, *article 32 of law No. 2007-248* was enacted mandating that 100% of the pharmacies in France participate in the collection of unused medicinal drugs (UMD) intended for human use that are returned by the general public (87). Prior to Cyclamed, the Extended Producer Responsibility (EPR) was enacted as law in 1992 to regulate the collection of packages from general household products and has since been extended to collecting pharmaceutical product packaging (French Environment and Energy Management Agency, 2015). On the 17<sup>th</sup> of June 2009, French decree no 2009-718 was instated to support the EPR, which outlines the process through which unused medicinal drugs are to be collected, treated, and disposed in France along with what parties are responsible for financing the system (89). The decree also asserts that in addition to the financial obligations, pharmaceutical companies must organize the systems necessary for the collection of unused medicinal drugs (UMD).

## **Financing**

Pharmaceutical companies are entirely responsible for covering all expenses required for Cyclamed to operate the systems required to collect, transport, incinerate, and dispose unused pharmaceutical household waste (87). The proportion that each drug manufacturer is required to contribute is based on each drug company's share of the pharmaceutical market, with a tax of €0.0022 being applied to each package of medication that is sold by a drug company (87). Sanofi has the largest pharmaceutical company in France with the greatest market share to date, and hence is responsible for the largest financial contribution to Cyclamed (90). The reported operational cost in 2014 was 7.14 million euros, predicted to rise to 10 million euros, partly due to the expected increase in volume of unused drugs that will be returned to pharmacies by consumers in the future (87). Cyclamed provided an expense breakdown for the 2017 fiscal year which indicated that 83% of the budget was spent on the process, which included collecting, transporting, and the safe destruction of pharmaceutical waste (87). One-tenth of the budget was spent on public awareness raising initiatives through television or social media advertisements (87). Just under five percent of the budget was spent on salaries for the employees involved in the process (87). Two percent of the budget was spent on research and development for quality assurance and improvement (87).

## **Public Awareness**

Since 1995, Cyclamed has utilized the services of the BVA Institute to administer an annual survey to study consumer behavioural as it relates to sorting and disposing unused medicinal drugs for people 18 years of age or older (91). Of the consumers surveyed in 2019, 80% had returned unused drugs to their local pharmacy for safe disposal and destruction (91). Women with children under the age of 15 were the most likely to return unused medicinal drugs to the pharmacy at 85% (91). The most common reasons for returning leftover medications to pharmacies were out of concern for health and safety in the home, while environmental concerns were secondary. These responses suggest that consumers may not be as informed about the environmental impacts that occur from improper drug disposal practices, or that people are more sensitive to the immediate health dangers rather than the indirect longer-term environmental health consequences. In 2019, 64% of people living in France said they knew about the Cyclamed program, up from 51% in the previous year. This increase was credited to additional efforts to promote awareness through television advertisement campaigns (91). This is evidence by the fact that almost half of the people that were familiar with Cyclamed had initially learned about it through a TV commercial (91). The second most common way to learn about Cyclamed was through interactions with the pharmacy staff (91). The third most common way people became aware of Cyclamed and the medication return process were by seeing posters displayed on the window or stickers on pharmaceutical products (91).

Cyclamed also partners with pharmaceutical companies, insurance companies, and community organizations to raise awareness of safe medication disposal practices. More specifically, they use a two-pronged approach to address pharmaceutical waste by promoting environmental stewardship and by promoting good habits in terms of medication storage at home to improve household safety (91). In line

with the environmental stewardship, patients are encouraged to sort and separate the medication packaging and its non-drug contents from the medications and dispose accordingly.

### **Monitoring and Oversight**

In 2014, there was approximately 12,056 tonnes of unused medicinal drugs collected and diverted away from the environment (87). In line with the environmental stewardship, Cyclamed harnesses and monitors the energy consumption involved in the collection, transportation, and disposal of pharmaceutical waste. Specifically, Cyclamed couples the process of energy recovery from its 55 units to the incineration of pharmaceutical waste such that it generates enough steam on average to provide heating and electricity to the equivalent of 7,000-8,000 homes each year (87). Cyclamed tracks its performance by monitoring the amount of waste and calculating the percentage change from year-to-year in order to determine the effectiveness of their public awareness campaigns geared to encourage the return of medications to pharmacies (87). Public awareness is also measured by tracking engagement with social media content, for example, the number of views on a social media post (e.g., Facebook or Twitter) and views on YouTube videos (87).

### **Sweden**

Established in 1971, Apoteket AB is a not-for-profit retail pharmacy chain and a state-owned monopoly under the Swedish Government's Ministry of Enterprise and Innovation. All pharmacies, including those situated in the community, and the healthcare setting such as hospital and clinics are operated by Apoteket AB (92). This unique infrastructure was instrumental for the country being able to achieve participation from all pharmacies in medication take-back programs (92).

### **Process**

When Apoteket pharmacies dispense prescriptions, customers are also issued a clear bag with instructional text, indicating how and where to return leftover medications (92). It is the responsibility of the consumer to sort and separate empty packages from medications, with the packages being disposed as per the requirements of each municipality. Once the unused medications are collected by the community or hospital pharmacy from the consumer, they are placed in the designated waste containers. According to Apoteket's Drug Waste Guide, pharmaceutical waste is sorted and placed in designated containers depending on the formulation of the drug — whether solid, liquid, or other (93). Once pre-packaged appropriately, they are placed in a destruction waste bin for drug waste (93). These packages are then transported to environmentally-friendly incineration facilities where the gases are cleaned prior to release into the atmosphere and the debris is dumped on designated leak-proof landfill sites (94). The Swedish Medical Products Agency (Läkemedelsverket) approximates that while 1,500 tonnes of unused medicines are collected and destroyed safely each year, estimates suggest there is still 250 tonnes of household waste that are improperly disposed through the toilet, down the sink or in regular garbage (95). Apoteket has recognized this reality and has actively integrated the collection and disposal of leftover medications into its Sustainability Plan (Figure 4).

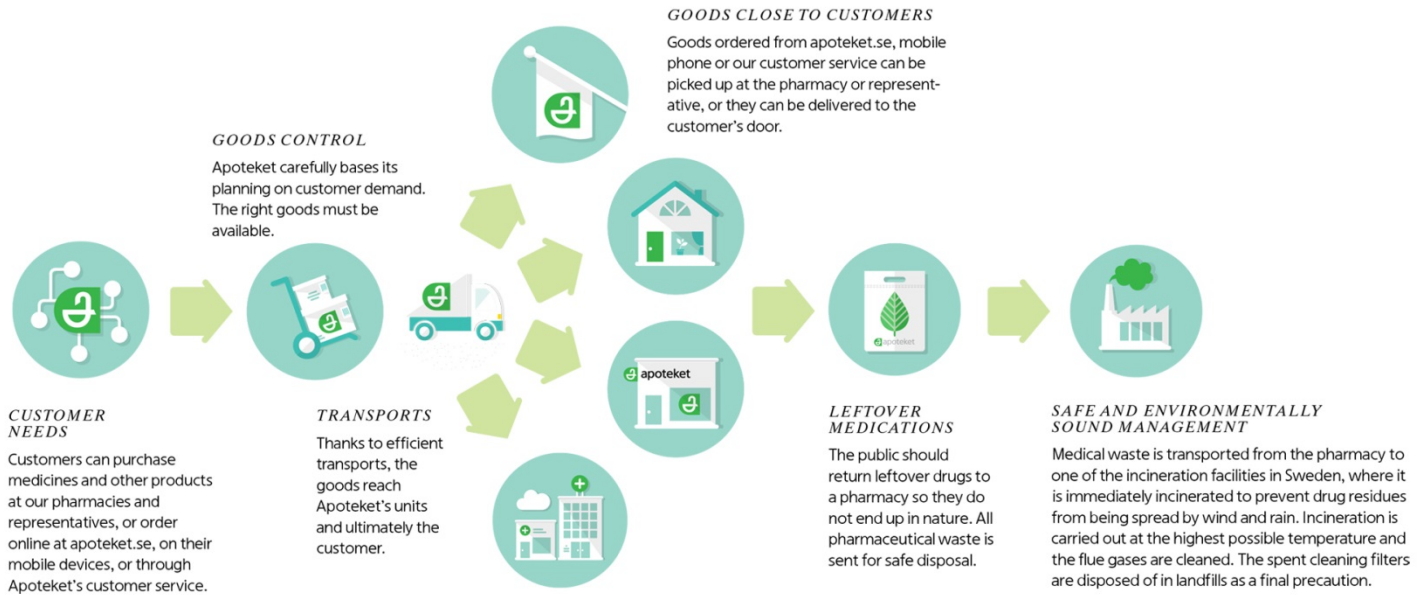


Figure 4: Source: Apoteket Annual and Sustainability Report 2015

## Financing

In Sweden, the medication take-back and disposal program is exclusively government funded. The annual cost of operating the collection and safe destruction of unused pharmaceutical drugs is approximately 1.4 million euros (92).

## Public Awareness

Section 8 of Regulation (2009:1031) on producer responsibility for medicines, when translated by Google Translator reads "A producer shall inform those who purchase medicines from the producer about the possibility of handing over waste which is the drug to the producer and why the waste should be handled in a special way." (96). This indicates that there are policies in place to hold pharmacies accountable for actively reminding patients to return unused medications to pharmacies. Also, recognizing the reasons people store unused medications in their home, Apoteket AB also focuses on initiatives to improve patient adherence to treatment regimens by counselling on the importance of completing a prescription regimen as directed by a healthcare provider (95). This is a systems-thinking approach to tackling the problem of unused medication storage and the potential harm to humans and the environment.

A 2015 survey by Apoteket AB highlighted that approximately 54% of customers return unused medications to pharmacies, an 11% increase from 2007 (92). This notable increase is partly due to the fact that members of the customer loyalty club receive environmental bonus points when they return leftover medication (92). Every year, between March 25<sup>th</sup> and April 30<sup>th</sup>, customers are eligible to

receive twice as many environmental bonus points when they return unused medications to their Apoteket pharmacy (92). Creating a reward system for consumers who return their unused household medications to the pharmacy for safe destruction creates a proxy indicator that can be used to monitor the population's attitudes and behaviour towards safe disposal practices.

### **Organization and Oversight**

Previously, retail pharmacies were allowed to operate privately, free from the control of the state (97). Since Health Canada published their report *Pharmaceutical Disposal Programs for the Public: A Canadian Perspective* in 2009, Sweden's pharmaceutical retail industry has once again undergone wholesale changes. As of July 1<sup>st</sup> of 2009, the Swedish pharmacy market was re-regulated as per new government policies, allowing privately companies to own and operate pharmacies in a new competitive free market (97,98). The government sold almost two-thirds of the state-owned stores to private companies, allowing them to re-brand, while other companies established new privately-owned pharmacy chains altogether (97,98). The result was an expansion of the retail pharmacy industry from about 950 stores to 1400 (99). The Swedish Medical Products Agency is responsible for monitoring and governing all pharmacies in Sweden. Despite a new regulation (2009: 1031)(96) on producer responsibility for medicines, which states that pharmaceutical retailers are required to accept and dispose of household pharmaceutical waste (96), it remains unclear whether this overhaul of the pharmacy landscape has disrupted the pharmaceutical waste disposal systems that were previously in place.

### **Comparative Analysis**

While there are no explicit standardized guidelines outlining a process for collecting, processing, and disposal of pharmaceutical waste, many countries in the EU have implemented at least some semblance of a collection and disposal system. *Article 127b* of *Directive 2004/27/EC of the European Parliament and of the Council* is an amendment of the previous version, *Directive 2001/83/EC on the Community code relating to medicinal products for human use* and now reads, "Member States shall ensure that appropriate collection systems are in place for medicinal products that are unused or have expired." (88). *Article 54* was also amended to read, "specific precautions relating to the disposal of unused medicinal products or waste derived from medicinal products, where appropriate, as well as reference to any appropriate collection system in place.." in relation to the labelling of medication packages (88). Despite these jurisdictional requirements mandating European states to manage pharmaceutical waste, the success of these systems is largely dependent on the public's awareness of these schemes, as many people continue to dispose of medications by flushing down the toilet, pouring down the sink, and discarding with regular household garbage (2).

France and Sweden both have legislation that essentially mandates that pharmacies collect unused and expired medications from consumers. In many other countries, each pharmacy has the option to choose whether to opt into their local, regional, or national pharmaceutical waste collection and disposal programs (Appendix B). One of the major differences in Sweden's Apoteket AB scheme is that they collect unused pharmaceutical drugs from both the community and healthcare setting, while France's

Cyclamed collects only drugs intended for human consumption from the general public. Furthermore, Cyclamed does not accept non-human drugs or any pharmaceutical waste from healthcare facilities. From the information that is publicly available in English, it is unclear whether Apoteket AB's drug collection and disposal system also applies to the new privately-run pharmacies or whether these pharmacies are independently responsible for handling the waste they collect. Despite some of these key differences, both countries recognize the importance of actively promoting awareness of these unused medication collection schemes by emphasizing the human and environmental health aspects. It is difficult to compare some European countries to Canada, since each province in Canada is separately responsible for operating waste management programs. Understanding the uniqueness of each country's process will provide insights into potential gaps and opportunities for improvement for each of Canada's provincial medication take-back-schemes or lack thereof.

## Discussion and Conclusion

The accumulation of antibiotics and other antimicrobial agents in the environment can contribute to AMR, the constant evolutionary modifications in viruses, bacteria, fungi, and other pathogens against standard antibiotics, antivirals, and antifungals.

Improper disposal of unused pharmaceutical drugs from households is a major contributor to environmental pollution and understanding the pathways through which pharmaceuticals enter the environment can provide insight into some mitigation strategies to prevent this current practice. Organized systems for the collection and disposal of unused or expired pharmaceutical products have the potential to divert pharmaceuticals from entering valuable ecosystems that are essential for life.

The effects of trace levels of drugs in the environment on humans have yet to be systematically measured and there are few published studies establishing a direct link between human health and pharmaceutical pollution in the environment. However, there is a great deal of evidence that pharmaceutically active substances do accumulate in water and soil. The potential for improperly disposed antibiotics to contribute to antimicrobial resistance therefore remains plausible, and there are examples for more cohesive pharmaceutical disposal that can be implemented across Canada as a precautionary measure.

The 2002 *Food and Drug Act* environmental assessment regulation survey highlighted that most Canadians appeared to link safe disposal of household waste with safety for children and other related health issues, rather than for reasons of environmental protection. The report also pointed to two major barriers for safe household disposal: a lack of information or education and inconvenient processes for returning unused medications (25).

Our review of evidence revealed gaps in the standardization and evaluation of best practices for medication return programs across Canada. This is at least in part due to the fact that policies and programs related to the environment and pharmaceutical waste management are administered at the provincial level. Consequently, there are different strategies and approaches adopted across provinces for disposing of pharmacologically active substances. Across Canada, this creates a fragmented – and potentially confusing – system as regulated drug disposal programs have only been implemented in four provinces – British Columbia, Manitoba, Ontario, and PEI – while others still lack regulated or formalized medication return programs. There are several organizations involved in the stewardship of safe disposal of health care waste, and in particular, pharmaceuticals. However, there is limited coordination across agencies or jurisdictions.

Pharmaceutical manufacturing plants contribute a great deal to environmental pollution through the discharge of residual pharmaceutical waste products generated by the manufacturing process into the surrounding receiving bodies. We found only two studies published in North America, indicating the need for further research. A study conducted in Ontario in 2019 highlighted that drugs such as antidepressants, analgesics, antibiotics, cardiovascular medications are discharged directly from the



point source which represents a key source of pharmaceutical pollutants to receiving sewer sheds. In addition, none of the five manufacturing plants analyzed in this study had on-site treatment facilities to filter pharmaceutical waste before discharging effluents to sewer (55). Presently in Canada, there are no metrics in place that would allow a study of the economic benefits of pretreatment water plants (73). This points to a gap in oversight of pretreatment at pharmaceutical manufacturing facilities to reduce sewage loadings to receiving treatment plants, product loss, which ultimately leads to environmental contamination.

Largely, there is a lack of Canada-wide policy research comparing different strategies implemented for the disposal of pharmaceuticals, highlighting the importance of centralized legislature and policy for pharmaceutical disposal. It is important to expand on environmental monitoring and environmental risk assessment on the level of pharmaceuticals of greatest concern to the environment so that a sewage treatment system can be designed for those specific compounds. This can also create an imperative for pharmaceutical manufacturers to develop the non-active ingredients of drugs from more environmentally friendly material to reduce the environmental burden, subsequently reducing the risk to animal and human health. At the same time, raising awareness and increasing adherence to medication regimens will significantly reduce pharmaceutical waste and simultaneously improve the management of waste. The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) has adopted a proposal to reinforce precautionary and safety measures on environmental aspects of medicines by including information on the package leaflet or on product summary to highlight potential environmental hazards (43).

Canada can learn from the well-coordinated efforts in EU countries to conduct surveillance of antibiotic resistance, the rate of human antibiotic use, as well as safe disposal strategies adopted by these nations such as drug classification based on an environmental impact risk assessment. This information will help prescribers and dispensers to select preferentially the least bio-accumulative interchangeable equivalent. In the same context, the 2014 Senate Standing Committee on Social Affairs, Sciences and Technology recommended that Environment Canada and Health Canada make public a list of pharmaceutical contaminants that are monitored by these government departments and also to furnish details on sampling and testing of freshwater, groundwater, and bio-solids, etc. In addition, it was the committee recommended that Health Canada elaborate its environmental assessment of approved drugs and utilization of information collected and to publicly report on levels of pharmaceutical contaminants detected through surveillance (4). A key difference in practices between the EU and Canada is that in this country environmental risks are assessed of the substances rather than the final product. This is critical as the individual substances or components are notifiable under the New Substances Notification Regulations (NSNRs) (43). Due to this approach, the cumulative risks of the included substances on the Domestic Substance List (DSL) are not effectively evaluated and do not undergo further assessment. Once registered with DSL, the amount of import, production, and consumption of these given substances can contribute to unregulated environmental risks in this country. Hence, a change in the system is needed to measure the total pollution load of pharmaceuticals in Canada. Substances already placed on the DSL that have already been detected in harmful concentrations in the environment should also be re-assessed on an urgent basis.

Another critical gap is a lack of obligation for physicians and patients to dispose of any sample packages (clinical evaluation packages) appropriately. Sampling Technologies Inc. (STI), a Nova Scotia firm has developed a program through which pharmaceutical representatives provide doctors with a pack of preprinted, branded cards called smart sample on the back of which physicians can fill out the patient's name and dose in a manner akin to writing a prescription. The patients then present the card to the local pharmacy, where a pharmacy staff dispensed medication free of cost with proper counselling. The pharmacist bills STI, which bills the pharmaceutical company. There is potential to use these encounters to reduce wastage (72).

To trace the carbon footprint of pharmaceuticals, Canada should follow guidelines from other countries. In England, the NHS Sustainable Development Unit (SDU) accounts and reports across pharmaceutical and medical device life cycles from manufacturing to usage and finally to disposal. The SDU has developed a list of top 20 pharmaceuticals causing the high greenhouse gas emissions (GHGE) accounting for about 60% carbon footprints which can then be targeted with waste reduction strategies (100).

According to Environment Canada in 2015, wastewater treatment plant effluent quality is monitored through the measurement of total suspended solids (TSS), carbonaceous biological oxygen demand (CBOD), or nutrient levels. As a regulatory requirement, neither antibiotics nor any resistance indicators are monitored (101). A recent study looking at both influent and effluent water samples from two different wastewater treatment plants, aerated lagoon (AL) and biological nutrient removal (BNR) plants, clearly showed the presence of antibiotics, with AL having a higher concentration of the two (101). Regulators in Canada should consider designing better wastewater treatment systems to remove the pharmaceuticals before being discharged. Efforts should also be made to establish guidelines that limit the amount of drugs allowed to enter the water supply. A similar idea was proposed by Dr. Sébastien Sauvé from Université de Montréal (35). Furthermore, the utilization of highly cost-effective techniques such as solid-phase micro-extraction (SPME) allows for easy sample processing and extraction with limited sample volume compared to solid-phase extraction (SPE) and will produce fruitful results in detecting antibiotics in the environment (102). Given that hospital systems are known contributors to pharmaceutical pollution, pretreating wastewaters from those types of sources for the removal of pharmaceutically active substances before they enter main municipal water supplies is a more cost-effective approach compared to treating surface water that has already been contaminated (73). Similarly, pharmaceutical manufacturing plants pretreating wastewater is a cost-effective and environmentally friendly way to prevent active substances from entering sewers. Active monitoring and assessment of pharmaceutical manufacturing facilities should be practiced at all sites across Canada.

While PAS are designed to perform essential therapeutic functions in humans, there are some PAS in which usage can easily be curtailed. For example, triclosan, a commonly used antibacterial agent in soaps, dish detergents, and toothpaste, has been found in Canadian water streams as well as in drinking water. The Health Canada, Canadian Medical Association, and the Canadian Paediatric Society does not recommend the use of antibacterial products in regular hand-washing products and have advocated for

the implementation of these recommendations that would prevent triclosan from polluting water systems (36).

A review of Health Canada's directions for the public on the disposal of medications revealed some limitations:

- a) The Health Canada's webpage instructs members of the public to dispose of unused or expired medications with regular household waste, which may lead consumers to believe that this garbage disposal strategy is the safest and most acceptable method for pharmaceuticals, where in reality these pharmaceutical substances end up in landfills.
- b) Secondly, it mentions that unused or expired medications should be returned to any pharmacy in Canada at any day of the year, whereas in reality there are only pharmacies participating in take-back programs in some provinces will accept unused and expired medications at all times.

## **Role of Prescribers and Dispensers**

Healthcare professionals can play an important role in reducing the amount of pharmaceutical agents used in Canadian homes. In a recent study, about 79% of Canadian patients filled a prescription for opioids after surgery when compared to 76% in the U.S., and only 11% in Sweden (103). Healthcare providers can alter their prescribing practices on analgesics and antibiotics as these agents are commonly prescribed for longer than recommended. Pharmacists can also be involved by advocating for the return of unused pharmaceuticals by adopting tighter control on dispensing and adjusting medications to curb the growing number of auto refills.

Public awareness and participation in medication return programs are integral for the successful implementation of medication stewardship programs where prescribers and dispensers have a shared responsibility to educate the public about safe and proper disposal strategies. Pharmacies should consider documenting the volume of waste to enhance surveillance and gather support to cover the costs of pharmaceutical waste disposal services while educating policy-makers about the importance of formal medication return programs in preventing environmental pharmaceutical pollution. Pharmacists can remind consumers to safely return unused or expired medications to the pharmacy.

The Canadian Coalition for Green Healthcare has developed a green office toolkit for clinicians and office managers to connect Canadian healthcare systems to resources and facilitate the development of best practices to 'go green' in healthcare. This toolkit highlights the importance of educating healthcare providers and patients regarding the proper disposal of pharmaceuticals (104).

## **Conclusion**

Considering that pharmaceutical drugs provide therapeutic benefits to human health and potentially detrimental effects on the surrounding ecosystem, surveillance systems need to be in place to monitor the consumption and disposal of these medicines. The best way to mitigate this risk is to regulate their environmental pathways at source through labeling of medicinal products and building public awareness

and understanding of risks associated with pharmaceutical products in the environment. The safe disposal of unused or expired medicines as an integral part of an effective proper disposal strategy of pharmaceuticals will prove beneficial to humans, animals, and the environment. Currently, Canada lacks a national guideline or program such as those implemented in Scandinavian regions, Australia, and other OECD countries. For instance, Sweden and Australia have a good monitoring process with comprehensive data. They have invested a lot of effort in awareness-building campaigns for consumers and health professionals. Their surveillance systems show promising diversion rates for household pharmaceutical waste from garbage, toilets, and sinks. Finally, for Canada, it is imperative to have a safe disposal management system for all stakeholders involved in the exposure of the environment to pharmaceuticals, in order to prevent environmental contamination.

In Canada, further harmonization across different programs and adopting best practices from jurisdictions can have fruitful outcomes. More focus and resource driven strategies are needed such as shifting towards environmentally safe pharmaceutical products and having a nationwide monitoring policy on environmental risk assessment for pharmaceutical products, especially antibiotics. Nevertheless, further study and consultation are needed to determine how to optimize the management of pharmaceutical waste. Canada will need a multipronged approach which is echoed also by Rachel Bard, then CEO for the Canadian Nurses Association that the federal government has a leadership role to set benchmarks, the provinces must endorse legislation to achieve those targets and healthcare facilities must-have process in place for compliance and implementation (75).

Like Europe, Canada needs to address environmental pharmaceutical pollution and the looming threat of AMR in order to achieve United Nations sustainable development goals, for clean water, good health, and well-being by ensuring strict mechanisms in place to divert pharmaceuticals being disposed of away from the environment.

## **Limitations**

Below are some major limitations of this evidence review:

- This review lacks viewpoints from major stakeholders who are policy drivers in the Canadian system.
- For this review, only articles published in English and full text assessed via the University of Manitoba websites were retrieved and reviewed which may have restricted our scope.
- Though a systematic process was followed in search strategy, however, this is not a systematic review so lacks the rigor of systematic review in the form of a meta-analysis.
- Another industry such as agriculture and veterinary aspect is not reviewed in this analysis.

## **Questions for future considerations**

During evidence collection for this review, a number of strong knowledge gaps were identified which are presented as pressing questions for readers which should spark further research and knowledge building discussions.

- Systematically pursuing the following questions will help to determine the scope of environmental pharmaceutical waste in Canada and ultimately whether it contributes to the emergence of antimicrobial-resistant strains of microorganisms. How are pharmaceuticals, particularly antibiotics, collected and disposed of in long-term care facilities across Canada?
- How is the antimicrobial pharmaceutical waste disposed of by the agricultural and livestock industry?
- What are the formal processes for the disposal of pharmaceutical waste in hospital systems across Canada?
- How do drug manufacturers handle and dispose of pharmaceutical waste that is generated by their facilities?
- At any given time, what percentage of the Canadian population is consuming pharmaceuticals and what percentage of those pharmaceuticals are antimicrobials?
  - What percentage of people complete their antimicrobial/antibiotics as prescribed for the full course?
  - What proportion have leftover unused medicines stored and what types or classes of medications are commonly stored in their household?
  - What proportion of Canadians regularly dispose of their unused pharmaceuticals?
  - What are Canadians' pharmaceutical disposal practices? What percentage of the population safely dispose of medications by returning to the pharmacy, and what proportion dispose of them in a sink or toilet?
  - What percentage of Canadians are aware of their regional or provincial medications return or disposal programs?
- How much medication or pharmaceutical waste is collected by pharmacies participating in medication return programs in each province of Canada?
  - What classes of pharmaceuticals are most commonly collected for disposal?
  - From a policy analysis perspective, does the rate of medication return differ in provinces with mandatory medication return programs compared to provinces with voluntary return programs?

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