FACETS
a multidisciplinary open access science journal

PERSPECTIVE

# A suggestion for evolution of Canada's health regulatory system

**Jessica White[a], and Gregor Reid[ab]***

[a]Lawson Health Research Institute, 268 Grosvenor Street, London, ON N6A 4V2, Canada; [b]Departments of Microbiology and Immunology and Surgery, Western University, London, ON N6A 3K7, Canada

*gregor@uwo.ca

## Abstract

Aspects of Canada's health regulatory system are currently being reviewed. This is timely, as the regulation and definition of drugs, foods, and natural health products (NHPs) is in need of revision to facilitate greater transparency and less ambiguity. A number of studies have illustrated the importance of a nutritious diet to prevent and manage chronic disease. Therefore, legislation surrounding food health claims needs to be adjusted so that it is more informative for disease prevention and, in some cases, treatment. Canada is modernizing the regulation of self-care products, under which NHPs, including probiotic products, are listed. With the growing appreciation for the role that microbes play in human health and the recognition that many foods, including those containing probiotic organisms, can prevent or mitigate disease, this provides an opportunity to reassess regulatory categories.

**Key words:** microbiome, probiotics, Health Canada, chronic disease





Citation: White J and Reid G. 2018. A suggestion for evolution of Canada's health regulatory system. FACETS 3: 45–60. doi:10.1139/facets-2017-0049

Handling Editor: Yann Joly

Received: May 3, 2017

Accepted: September 25, 2017

Published: January 25, 2018



Published by: Canadian Science Publishing

## Introduction

The Canadian health regulatory system has evolved since the introduction of the Food and Drugs Act in 1920 to protect the public and prevent the sale of adulterated drugs (Health Canada 2007a). Despite major changes to the regulation of drugs, foods, and natural health products (NHPs) to ensure public safety, there are still a number of problems within the system. Too many drugs and NHPs reach the market only to be recalled by Health Canada because of adverse reactions or misinformation (Government of Canada n.d.).

During the past 20 or so years, there has been a growing appreciation for the influence of the human microbiome and its associated metabolites on many aspects of general health, digestion, and drug uptake in the gut. The delivery of microbes in the form of probiotics and fermented foods is becoming commonplace in Canada, as a growing number of probiotic products are available to the consumer (Skokovic-Sunjic 2016). Since Canada is currently modernizing the regulation of self-care products (Health Canada 2017a), it is an opportune time to reevaluate aspects of the mission and operation of Health Canada's regulatory system.

Currently, Canada's regulatory system defines a drug as any substance that prevents, treats, cures, or mitigates a disease (Canadian Food Inspection Agency 2003; Farrell et al. 2009). We believe that a policy change is needed to allow manufacturers to make similar claims for certain foods and NHPs without being forced to undertake the extensive documentation required for chemical

compounds such as drugs. However, all products must still be reviewed, with consumer safety as the foremost consideration.

The aim of this paper is to propose ways in which policy relating to health claims on foods and probiotics can become more informative and less ambiguous (Sanders et al. 2014).

## History and timeline of Canada's regulatory system

In 2017, Canada's federal government is divided into three branches (**Fig. 1**): legislative, executive, and judicial. Under the executive branch is the Cabinet, including the Minister of Health, whose portfolio encompasses the Canadian Food Inspection Agency (CFIA) and Health Canada. Within Health Canada is the Health Products and Food Branch (HPFB), which includes the following directorates: the Natural and Non-prescription Health Products Directorate (NNHPD), the Therapeutic Products Directorate (TPD), and the Food Directorate (Health Canada 2017b).

A number of events have influenced the federal government to modify the ways in which foods and drugs are regulated to ensure the safety of the public. **Table 1** includes a timeline of how the Canadian regulatory system has changed over the past century.

## Regulatory framework for foods, drugs, and NHPs in Canada

The Food and Drug Administration (FDA) of the United States of America defines drugs as substances used for "the diagnosis, treatment, mitigation or prevention of a disease, disorder, abnormal physical state or its symptoms . . . " or for "restoring, correcting, or modifying organic functions", a definition accepted by Health Canada (Canadian Food Inspection Agency 2003, p. 8-5). Foods are defined as "any article manufactured, sold, or represented for use as food or drink for human beings, chewing gum, and any ingredient that may be mixed with food for any purpose whatsoever" (Food and Drug Act 1985, p. 3). The NHP category comprises "vitamins and mineral supplements, homeopathic medicines, herbal therapies, traditional medicines, amino acids, probiotics, and certain personal care products" (Smith et al. 2014, p. 507). Although foods, drugs, and NHPs are all regulated by the federal government, the pathways and criteria by which they are regulated differ (Farrell et al. 2009).

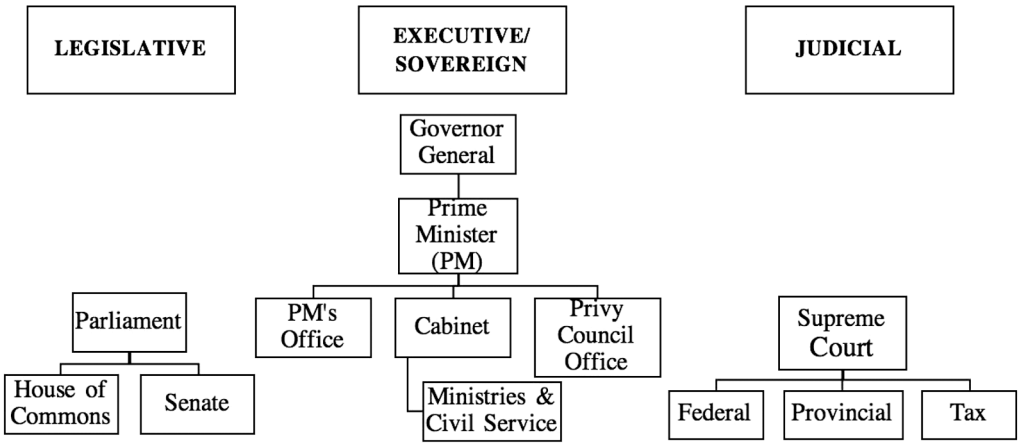


**Fig. 1.** The structure of Canada's federal government (Government of Canada 2016).

**Table 1.** Timeline of events in the history of Canada's health regulatory system.

| Year | Event | Reason or outcome | Reference |
|---|---|---|---|
| 1909 | Proprietary or Patent Medicine Act | Registration of medication to protect the public | Health Canada 2007b |
| 1919 | Creation of the federal Department of Health | To take charge of federal health functions such as food and drug standards | Dickin 2006 |
| 1920 | Food and Drug Act | During the late 1920s, requirements were created for drug licensing | Health Canada 2007b |
| 1947 | Revisions to the Food and Drug Act | Created many regulations in place today | Health Canada 2007b |
| 1951 | New Drug Submission for manufacturers | Required prior to the marketing of a drug | Health Canada 2007b |
| 1960 | Revisions to the Food and Drug Act | Thalidomide tragedy causing infant mortality | Health Canada 2007b |
| 1986 | Bill C-22 | Alteration to patent protection | Vandergrift and Kanavos 1997 |
| 1993 | Patented Medicines Notice of Compliance | North American Free Trade Agreement and Trade-Related Aspects of Intellectual Property Rights | Bouchard 2011 |
| 1997 | Closure of in-house laboratories | To prevent conflicts of interest | Kondro 2000 |
| 1998 | Notice of Compliance no longer a law, rather a policy | To accelerate approval for life-saving drugs | Lexchin 2007 |
| | Standing Committee on Health | Proposed a separate regulatory body for natural health products[a] | Parliament of Canada 1998 |
| | Compliance and Enforcement Strategy | To prevent the selling of unapproved traditional medicines | Jepson 2002 |
| 2000 | Health Protection Branch to regulate food and drugs | Lack of public confidence | Kondro 2000 |
| 2002 | Health claims | Disease risk reduction claims allowed for the first time in Canada | Hobbs et al. 2014 |
| 2004 | Natural health product regulations under the Food and Drug Act | To regulate manufacturing, packaging, labelling, storing, importation for sale, distribution, selling, and human clinical trials | Farrell et al. 2009 |
| 2006 | Blueprint for Renewal | To modernize Canada's regulatory system | Health Canada 2009a |
| 2007 | Blueprint for Renewal II | To address health claims, policies, and food contributors to chronic disease | Health Canada 2007c |
| | Drug Safety and Effectiveness Network | To connect and enable researchers across Canada to conduct post-market research separate from the pharmaceutical industry | Collier 2010 |
| 2008 | Canada Consumer Product Safety Act; amended Food and Drug Act | To strengthen rules on food, drug, and product safety | Elliott 2008 |
| 2009 | Generic medicines approved under Notice of Compliance | To avoid providing branded manufacturers with an advantage if they had not met conditions | Law 2014 |

[a]Prior to the establishment of NHPs, everything including food was regulated as a drug (Hobbs et al. 2014).

Drugs are regulated under the HPFB by the TPD. A manufacturer must obtain a license, and a specific protocol must be followed to ensure the benefits of the drug outweigh its risks (**Fig. 2**). This process invariably begins with the submission of a Clinical Trial Application (Health Canada 2010). After the clinical trial stage, a New Drug Submission must be completed, which is reviewed within approximately 300 days (Rawson 2015). Subsequently, the drug becomes available to the public and undergoes post-market surveillance so that any adverse reactions can be detected (Health Canada 2010).

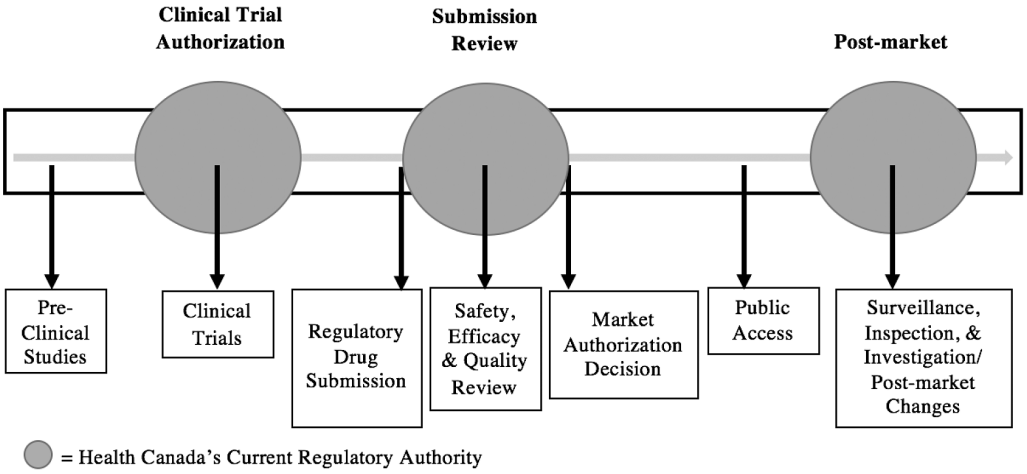


**Fig. 2.** Submission process for drugs entering the Canadian market (Health Canada 2007b).

However, in specific circumstances this process can be expedited, such as in the case of treatments for life-threatening conditions. Priority review was established so that patients suffering from a debilitating disease would have faster access to a drug they need (Health Canada 2012). This type of review follows the same process described above, but instead of a 300-day review period, the New Drug Submission will be reviewed within 180 days (Rawson 2015).

NHPs are regulated under the HPFB by the NNHPD and undergo a submission and review process similar to that for drugs (Food and Drug Act 1985; Natural Health Products Regulations 2003). Although NHPs are not considered drugs, they are regarded as a subcategory of drugs for regulation purposes. Therefore, any human clinical trials for drugs or NHPs require authorization from Health Canada. Applications for clinical trials involving NHPs, however, are typically approved within 30–60 days. For traditional medicine, such as Chinese medicine, proof of historical use within a specific culture is considered sufficient to demonstrate safety and efficacy. However, for nontraditional medicine, such as other types of NHPs, scientific evidence from clinical trial data is required (Farrell et al. 2009).

Regulations pertaining to NHPs include product licensing, which uses a three-tier system to determine the level of regulatory oversight prior to marketing (Office of Natural Health Products (Canada) 2000; Smith et al. 2014). A site license is also required before manufacturing, importation, and packaging can take place. Producers of NHPs must adhere to good manufacturing practices, follow labelling and packaging standards, and report any adverse reactions to the product within 15 days (Office of Natural Health Products (Canada) 2000; Nestmann et al. 2006).

The review process for an NHP can be expedited by referring to a monograph that describes the scientific evidence supporting the product (Health Canada 2017c). Three types of health claims are permitted on NHPs: therapeutic, risk reduction, and structure–function claims (Government of Canada 2006). Claims for disease treatment, prevention, mitigation, and cure are permitted only for drugs. The NNHPD is responsible for evaluating NHP health claims with regard to strength, quality, and credibility. Two examples of structure–function claims that are used on probiotic products in the US are "supports immune function" and "supports healthy intestinal balance" (Sanders 2003, p. 96; Farrell et al. 2009, p. 390). Interestingly, these two examples state a general effect, which is not recommended in Canada. Instead, claims such as "promotes regularity" and "aids in digestion" are more specific and therefore acceptable (Health Canada 2009d, p. 4).

Table 2. Current claims permitted on foods in Canada and their dates of acceptance.

| Food or nutrient(s) | Claim | Year approved |
|---|---|---|
| Low sodium and high potassium | Reduces the risk of high blood pressure | 2000 |
| Vitamin D and calcium | Reduces the risk of osteoporosis | 2000 |
| Low saturated and trans fat intake | Reduces the risk of heart disease | 2000 |
| Consumption of fruit and vegetables | Reduces the risk of certain types of cancer | 2000 |
| Psyllium | Lowers cholesterol | 2011 |
| Phytosterols | Lowers cholesterol | 2010 |
| Oat fiber | Reduces the risk of heart disease | 2010 |
| Barley products | Lowers cholesterol | 2012 |
| Unsaturated fat | Lowers cholesterol | 2012 |
| Sugar-free chewing gum | Reduces the risk of dental caries | 2014 |
| Ground whole flaxseed | Lowers cholesterol | 2014 |

In our view, the Canadian system is more advanced than the FDA's; however, further improvements are warranted. Vague and generalized claims are not informative for consumers and patients and, when found on many products, can be confusing. More specific claims and inclusion of the evidence in support of such claims would help the end user to differentiate between products.

The regulatory oversight of foods differs from that of NHPs and drugs. Health claims on foods are regulated and governed by Health Canada and the CFIA to ensure food labels are accurate and not misleading (Canadian Food Inspection Agency 2017a, 2017b). Health Canada also permits disease risk, therapeutic, and structure–function claims on foods, with the exception of claims directed towards children under the age of two or claims regarding low-energy diets (Canadian Food Inspection Agency 2017a). Food manufacturers must comply with a more stringent list of rules pertaining to the claims that are made. Again, food claims cannot state that the product will prevent, treat, cure, diagnose, and (or) mitigate a disease, as this definition is used strictly for drugs (Sanders 2003). So far, there are 11 disease risk reduction and therapeutic claims allowed on foods in Canada (**Table 2**) (Health Canada 2017d). Interestingly, sugar-free products have been shown to disrupt the host microbiome (Suez et al. 2015), yet no such warning is given to consumers.

If a company wants to use a new claim, it must apply to Health Canada and have its documentation evaluated based upon three main criteria: causality, generalizability, and quality assurance (Health Canada 2009c). There must be a relationship between the food and the specified health benefit, which must be supported by scientific evidence from human clinical trials (Health Canada 2011a). Unlike drugs, NHPs, and novel foods, regular food items do not require post-market surveillance (Farrell et al. 2009). However, in the US, probiotic research involving human subjects is discouraged mainly because regulators view probiotics as drugs (Sanders et al. 2016). This is even more so the case in Europe, where the European Food Safety Authority has banned the use of the term "probiotic" and has failed to approve any claim despite the overwhelming clinical data underlying Health Canada's approval of claims (Sanders and Levy 2011).

## Issues within the current regulatory framework

There are a number of deficiencies and ambiguities within Health Canada's current regulatory framework that need to be addressed. Many gaps are the result of a decentralized health care system, a lack

of transparency, and insufficient communication. The federal government distributes funds to each of the provinces (Vandergrift and Kanavos 1997). However, provinces differ on the standards by which they regulate drugs (Jepson 2002). Health Canada relies on industry to self-regulate and report (Stanbrook and Killeen 2012); as a result, many provinces are heavily reliant on information submitted by companies to Health Canada. However, there can be gaps in the information disseminated by Health Canada to the provinces, and a lack of transparency. Provincial regulators are not provided with full access to the preclinical and clinical trial data that drug sponsors submit, unless the company agrees to release the data. This creates problems when provinces are establishing drug benefit plans because they must depend solely on Health Canada to provide accurate and complete information. More populous provinces, such as Ontario, are at an advantage because they have more financial resources and thus have greater power to request more information when establishing a drug benefit list. In contrast, smaller provinces are more dependent on Health Canada when making decisions regarding their provincial drug list.

It has been reported that many provincial officials lack confidence in Health Canada because clinical trials are short in duration, have small sample sizes, and lack a comparison with other active ingredients and because the safety information made public may not accurately depict the harms associated with a drug (Lexchin et al. 2013). This is illustrated by the number of drugs pulled off the Canadian market because of safety issues (Lexchin 2010). Some provincial officials are also concerned about how adverse reactions are being reported (Lexchin et al. 2013). The Canadian Medical Association has claimed that the TPD does not provide acceptable warning of potential adverse reactions (Wiktorowicz 2003). Health Canada has also stated that if no further changes are to be made to the drug and it does not cause any adverse effects, it may never have to be reviewed again (Health Canada 2007a). These positions are partly due to limited regulatory staff and a system that does not overly delay the approval of drugs. One might think that companies would sufficiently assess the safety of a product before its approval and restrict its prescribed use so that adverse outcomes are rare occurrences. However, in many instances, safety is assessed using animal models, often rodents and rabbits (Akhtar 2015). Such practice requires reconsideration, as in too many instances, animals poorly simulate the human condition or are sacrificed to satisfy a requirement rather than to truly add substance to the safety and efficacy profiles (Akhtar 2015).

Another issue arises from post-market surveillance. Once a manufacturer markets a drug, it has few obligations, as Health Canada does not require long-term safety and efficacy evaluations post-market (Yeates et al. 2007). There have been a number of documented incidences in which pharmaceutical companies have not been forthcoming with safety information (Lurie and Wolfe 2005). In recent years, long-term antibiotic use, particularly in the young, has been shown to have adverse health outcomes (Cox and Blaser 2015), yet no pharmaceutical company has faced regulatory consequences. The presence of antibiotics and a range of other drugs in drinking water is now widely reported (Cox and Blaser 2015; Khan et al. 2016), presumably owing to urinary excretion. To date, the producers of these chemicals have not been held accountable for proper disposal of their products. The same is true for a wide range of chemicals, including pesticides and heavy metals, that find their way into drinking water systems and the food chain, likely to the detriment of humans. At the very least, this is an ethical issue worthy of further discussion and public debate.

Although NHPs are subject to regulatory standards and practices similar to those that apply to drugs, 60% of NHPs analyzed have been considered unsatisfactory according to post-market surveillance data. The major areas of concern are poor quality, contamination, adulteration, and misleading advertising (Smith et al. 2014).

In terms of foods, the situation is confusing for consumers because food companies add vitamins, probiotics, omega-3 fatty acids, and herbal ingredients to foods, classifying them as "functional

foods". However, these ingredients, prior to being added to food, are considered NHPs and are regulated as such (Farrell et al. 2009). In addition, the Food Directorate requires that foods contain a nutrition facts table, ingredient list, and allergen list, but this requirement differs for NHPs (Health Canada 2009b).

Some of the issues raised here are complex and will require public discussion, at the very least, along with internal review by Health Canada. With the current review of self-care products, there is an opportunity to extend the review process to assess why more informative claims are permitted only for drugs and why so-called safety assessments lead to animals being sacrificed when they often do not relate to the human condition. However, the fear amongst researchers is that Health Canada is moving more towards FDA regulations, which is ironic because it is generally considered ahead of its American counterpart in creating informative procedures.

## How does Health Canada's approach compare with those of the FDA and the European Union?

Although Canada and a number of other countries have similar regulatory protocols, there are some major differences worth discussing. In terms of numbers of clinical trials conducted, Canada is ranked third behind the European Union (EU) and the US (Government of Canada 2001). The FDA has a review period of about 50 days (Downing et al. 2012), whereas Health Canada's review period is 300 days (Rawson 2015). Canadian submissions experience an average delay of 540 days compared with 106 days for submissions to the FDA in the US and 215 days for submissions to the European Medicines Agency in the EU (Shajarizadeh and Hollis 2015a). The time between drug submission and approval is about 3 months longer in Canada than in the US (Ezeife et al. 2015).

In terms of whether a new drug submission receives priority review, a major determining factor is the resources available (Rawson 2002). The US has one of the most powerful and influential pharmaceutical industries in the world (Lexchin and Gleeson 2016). The massive lobbying efforts of this industry are believed to result in, for example, oncology therapies in the US being much more likely to receive priority review than the same therapies in Canada.

Generally speaking, Canada and the US are in agreement regarding drugs that should not receive priority review (Rawson 2002). In both countries, there is the expectation that drugs should be safe, efficacious, and priced in a manner that is fair and supportive of research and development. However, consumers pay far more for drugs in the US than in other countries, leading to accusations of price gouging (Shajarizadeh and Hollis 2015b). In Canada, low drug prices are emphasized, whereas in the US, the focus is on protecting patent rights (Hollis and Ibbott 2006).

The FDA is either less rigid or not suitably placed to adjudicate in terms of regulatory oversight of dietary supplements, as some NHPs have been used in the treatment of cancer (Ehrenpreis et al. 2013). Structure–function claims on NHPs in the US do not require premarket approval, and new health claims are more welcome in the US than in Canada (Hobbs et al. 2014).

The EU has completely banned the use of antibiotics to promote weight gain in animals for human consumption, and it claims that this has not affected production or profits (Wegener 2003). In 2005, both the US and the EU adopted a risk management approach to drug safety. In the US, under the False Claims Act, if a company fails to report adverse reactions to a drug, it can face charges. The 2007 amendment to the Food and Drugs Act revised the Prescription Drug User Fee Act so companies would conduct post-market surveillance. As a result, the FDA can enforce changes to drug labels and require risk evaluations not only for new drugs on the market but also for existing drugs (Silversides 2010).

The regulatory system in the EU is fairly complex, which limits the number of disease risk reduction claims allowed on foods. Supplements such as vitamins and minerals are considered a food in the EU, whereas they are considered an NHP in Canada (Hobbs et al. 2014). In Europe, health claims on food labels are based upon "generally accepted scientific evidence" and undergo assessment to determine their truthfulness (Glanville et al. 2015, p. 6).

## The pharmaceutical industry

The shortage of new drug classes and the increasing problem of antibiotic resistance are major global concerns (Stanbrook and Killeen 2012). Companies claim that the cost of creating a new drug is exorbitant (over $860 million) (Wood 2006; Bouchard 2011), but in their calculations they include the cost of multiple failures of drugs in phases 1 to 4. Perhaps if more caution was exercised before embarking on expensive studies, the failure rate would be lower and the average cost of taking drugs to market would decrease. In many instances, companies develop "me-too" drugs that are barely an improvement on existing ones. Clearly, companies need to devise new approaches to drug development, and government policy and legislation could provide some incentives for innovation (Bouchard 2011).

In 2003, Canadians spent $20.1 billion on pharmaceuticals (Guindon and Contoyannis 2012). Tens of billions of dollars are spent by pharmaceutical companies on direct advertising to American consumers and health care providers, which helps to keep net profits high (Gagnon and Lexchin 2008). These advertisements are invariably seen by Canadian consumers (Government of Newfoundland and Labrador 2004). Many physicians rely on pharmaceutical companies to provide reliable and accurate information about the drugs they are promoting (Rapoport 2005). Unfortunately, trustworthy information is not always relayed when the goal is to maximize profits. Some misconduct may be evident in how pharmaceutical sales representatives (PSRs) obtain their information and sell their products. Information delivered to physicians by PSRs is often misleading (Lexchin and Kohler 2011) and accompanied by free product samples (Mintzes et al. 2013). Social science research suggests that when individuals are given free products, they are more strongly influenced by those products and are more willing to advocate their use (Brennan et al. 2006). When physicians were interviewed regarding their experience with PSRs, the results indicated that there was a major lack of information regarding the risks of the products, as the benefits were mentioned twice as often (Mintzes et al. 2013). This is a violation of law according to Health Canada, which states that "messages cannot emphasize only product benefits without included safety information" (Health Canada 2011b, p. 1). Furthermore, there is concern about the accuracy and truthfulness of information on pharmaceutical websites (Kim 2015).

The potential detrimental effects of drugs on human health are evident from the thalidomide tragedy in Canada in the 1960s. Based on an American statistic, approximately 81 of 170 million pharmaceutical users experience adverse reactions each year (Light et al. 2013). A number of drugs that have made it to the Canadian market have later been recalled. For example, rofecoxib (Vioxx), a COX-2 inhibitor, was shown to increase the risk of cardiovascular events despite no evidence of this risk during the initial clinical trial stage (Sibbald 2004). The addictive qualities of codeine have led to gastrointestinal problems because codeine is frequently sold in combination with nonsteroidal anti-inflammatory drugs (MacKinnon 2016). In 1996, Health Canada approved the sale of OxyContin, which was used to relieve pain; however, the drug had no warning label outlining its addictive potential, and many negative health consequences have resulted because of its addictive nature (Lexchin and Kohler 2011). Hydroxycut, a weight loss medication, has been associated with hepatoxicity (Chen et al. 2010; Garcia-Cortes et al. 2016). Even some NHPs have been shown to have adverse effects (Nestmann et al. 2006); for example, green tea extracts and vitamin A supplementation have been associated with hepatoxicity (Garcia-Cortes et al. 2016).

Another concern is the number of drug manufacturing companies that have moved to foreign countries because of lower costs. Many drugs are being imported and often contain ingredients that are restricted in the US or Canada (Pew Health Group 2011). The quality of these foreign-made drugs is thus open to question, despite best intentions and ongoing monitoring.

## The influence of microbes on drugs and health

Microbes are critical for human development, and disruption of the microbiota—for example, with antibiotic use in early life—can later prove detrimental. Drugs can modify the gut microbiota, and likewise their activity can be altered by microorganisms. In an extreme illustration, antibiotic exposure at a young age can increase the likelihood of developing a chronic disease such as type 2 diabetes (Yallapragada et al. 2015). More than half of all antibiotic prescriptions are given to children aged 0–4 years (Yallapragada et al. 2015). In contrast, a nutritious diet including pre- and probiotics can prevent the onset of some chronic diseases (Delzenne and Bindels 2015; Kitazawa et al. 2015).

The issue of microbes and drugs is relevant for regulatory agencies on at least three counts. First, it should increase the duration of post-market monitoring for adverse events. Clearly, the long-term detrimental effects of antibiotics were not predicted when the drugs were introduced (Jernberg et al. 2010), and removing them from the market would be problematic, especially because no new antibiotic classes are emerging. Second, the human microbiome influences drug uptake (Haiser et al. 2013; Spanogiannopoulos et al. 2016), yet there is no regulatory requirement to test this or to alert physicians to the potential for drug levels to be higher or lower than anticipated because of the patient's microbiome. The use of probiotics may actually improve drug efficacy (Martinez et al. 2009a, 2009b), again raising the question of how one might make a claim that a probiotic has a drug-like effect. This would be particularly interesting if fermented foods also influenced drug uptake because of their bacterial content. Third, the overuse and abuse of antimicrobial agents extends to their inclusion in many over-the-counter products. The banning of triclosan and other antimicrobial chemicals in soap by the FDA in 2016 recognized that there is a fine line between countering infectious diseases and overdoing the killing of microbes (FDA 2016).

## A proposal moving forward

It is our view that it is an opportune time for regulatory authorities worldwide to allow disease prevention, treatment, and cure claims on certain foods and probiotic products without categorizing them as drugs and requiring producers to provide the same amount of evidence. By their very nature, drugs are chemical agents, which for the most part are not naturally occurring compounds with a safe history of use in humans. Certain foods are well known to prevent and treat disease; for example, scurvy, which results from an inadequate intake of vitamin C, can be overcome by the consumption of vitamin C-rich foods such as oranges (Jepson 2002). Many probiotic microbes are naturally occurring biological entities propagated to be delivered in sufficient numbers to confer a health benefit.

Health Canada has an opportunity to continue to do things better than the FDA, which has failed to accept the FAO/WHO definition of probiotics, or the EU, which shows no understanding of probiotics, has not developed appropriate policies to encourage research and development of probiotics, and has failed to create a body with suitable expertise to adjudicate claims made in applications for probiotic foods (Guarner et al. 2011). For more than 70 years, claims for disease prevention, treatment, mitigation, and cure have been allowed only for drugs. With our improved knowledge of foods, and particularly microbes in fermented foods or isolated from them, a mechanism should be devised to allow disease claims that are informative to consumers. This should extend to certain probiotic strains with a long history of safe use in humans. The clearer the information on labels for defined foods and probiotics, the easier it will be for consumers to know what they are buying and what they

can expect from the product. This will increase the documentation provided by manufacturers and lead to some products not being permitted to be called probiotic. Commentary on the current Health Canada discussion on self-care products has suggested that smaller companies cannot afford to perform human studies to test their probiotic or food products. This is unfortunate, but if companies want to take advantage of consumer demand for probiotics, then appropriate human studies should be conducted, or the company should not use the term "probiotic". Such studies need not require the level of funding required for studies of new drugs.

In addition, although safety must remain a primary driver of regulatory affairs, the needless sacrifice of animals must be reconsidered. Often, studies on rodents and rabbits are performed because of the request of regulators to show safety. But all too often, these models and studies are irrelevant or misleading because they are not applicable to humans (Shanks et al. 2009; Hayden 2014).

The changes we propose will require careful consideration by Health Canada and perhaps even public discussion. However, we do not agree with the argument that academics, industry, regulators, and consumers are different entities. All are end users who deserve high-quality products that have been appropriately tested for safety and clinical efficacy and labelled in a manner that is informative and clear.

## Author contributions

JW and GR conceived and designed the study. JW and GR performed the experiments/collected the data. JW and GR analyzed and interpreted the data. JW and GR contributed resources. JW and GR drafted or revised the manuscript.

## Competing interests

The authors have declared that no competing interests exist.

## Data accessibility statement

All relevant data are within the paper.

## References

Akhtar A. 2015. The flaws and human harms of animal experimentation. Cambridge Quarterly of Healthcare Ethics, 24: 407–419. PMID: 26364776 DOI: 10.1017/S0963180115000079

Bouchard RA. 2011. I'm still your baby: Canada's continuing support of U.S. linkage regulations for pharmaceuticals. Marquette Intellectual Property Law Review, 15(1): 71–146 [online]: Available from scholarship.law.marquette.edu/cgi/viewcontent.cgi?article=1166&context=iplr.

Brennan TA, Rothman DJ, Blank L, Blumenthal D, Chimonas SC, Cohen JJ, et al. 2006. Health industry practices that create conflicts of interest: a policy proposal for academic medical centers. Journal of the American Medical Association, 295(4): 429–433. PMID: 16434633 DOI: 10.1001/jama.295.4.429

Canadian Food Inspection Agency. 2003. Guide to food labelling and advertising [online]: Available from alimentheque.com/divers/GuideFoodLabellingAdvertising_CFIA_dec2011.pdf.

Canadian Food Inspection Agency. 2017a. Food labelling for industry [online]: Available from inspection.gc.ca/food/labelling/food-labelling-for-industry/eng/1383607266489/1383607344939.

Canadian Food Inspection Agency. 2017b. Food labelling and advertising [online]: Available from inspection.gc.ca/food/labelling/eng/1299879892810/1299879939872.

Chen GC, Ramanathan VS, Law D, Funchain P, Chen GC, French S, et al. 2010. Acute liver injury induced by weight-loss herbal supplements. World Journal of Hepatology, 2(11): 410–415. PMID: 21173910 DOI: 10.4254/wjh.v2.i11.410

Collier R. 2010. Post-market drug surveillance projects developing slowly. Canadian Medical Association Journal, 182(1): E43. PMID: 19901045 DOI: 10.1503/cmaj.109-3103

Cox LM, and Blaser MJ. 2015. Antibiotics in early life and obesity. Nature Reviews Endocrinology, 11: 182–190. PMID: 25488483 DOI: 10.1038/nrendo.2014.210

Delzenne NM, and Bindels LB. 2015. Gut microbiota: *Ganoderma lucidum*, a new prebiotic agent to treat obesity? Nature Reviews Gastroenterology & Hepatology, 12(10): 553–554. PMID: 26284561 DOI: 10.1038/nrgastro.2015.137

Dickin J. 2006. Public health [online]: Available from thecanadianencyclopedia.ca/en/article/public-health/.

Downing NS, Aminawung JA, Shah ND, Braunstein JB, Krumholz HM, and Ross JS. 2012. Regulatory review of novel therapeutics—comparison of three regulatory agencies. The New England Journal of Medicine, 366(24): 2284–2293. PMID: 22591257 DOI: 10.1056/NEJMsa1200223

Ehrenpreis ED, Kulkarni P, Burke C, and the FDA-Related Matters Committee of the American College of Gastroenterology. 2013. What gastroenterologists should know about the gray market, herbal remedies, and compounded pharmaceuticals and their regulation by the food and drug administration. The American Journal of Gastroenterology, 108: 642–646. PMID: 23644956 DOI: 10.1038/ajg.2012.348

Elliott I. 2008. Canada to tighten food, drug laws. Feedstuffs, 80(15): 4.

Ezeife DA, Truong TH, Heng DY, Bourque S, Welch SA, and Tang PA. 2015. Comparison of oncology drug approval between Health Canada and the US Food and Drug Administration. Cancer, 121(10): 1688–1693. PMID: 25604014 DOI: 10.1002/cncr.29246

Farrell J, Ries NM, Kachan N, and Boon H. 2009. Foods and natural health products: gaps and ambiguities in the Canadian regulatory regime. Food Policy, 34(4): 388–392. DOI: 10.1016/j.foodpol.2009.01.002

FDA. 2016. FDA issues final rule on safety and effectiveness of antibacterial soaps [online]: Available from fda.gov/newsevents/newsroom/pressannouncements/ucm517478.htm.

Food and Drug Act. 1985. R.S.C., c. F-27 [online]: Available from laws-lois.justice.gc.ca/eng/acts/F-27/.

Gagnon MA, and Lexchin J. 2008. The cost of pushing pills: a new estimate of pharmaceutical promotion expenditures in the United States. PLoS Medicine, 5(1): e1. PMID: 18177202 DOI: 10.1371/journal.pmed.0050001

García-Cortés M, Robles-Díaz M, Ortega-Alonso A, Medina-Caliz I, and Andrade RJ. 2016. Hepatotoxicity by dietary supplements: a tabular listing and clinical characteristics. International Journal of Molecular Sciences, 17(4): 537. PMID: 27070596 DOI: 10.3390/ijms17040537

Glanville J, King S, Guarner F, Hill C, and Sanders ME. 2015. A review of the systematic review process and its applicability for use in evaluating evidence for health claims on probiotic foods in the European Union. Nutrition Journal, 14(16): 1–9. PMID: 25889449 DOI: 10.1186/s12937-015-0004-5

Government of Canada. 2001. Canada Gazette Part II, 135(13): 1084–1232 [online]: Available from publications.gc.ca/gazette/archives/p2/2001/2001-06-20/pdf/g2-13513.pdf.

Government of Canada. 2006. Evidence for safety and efficacy of finished natural health products [online]: Available from publications.gc.ca/site/eng/9.650466/publication.html.

Government of Canada. 2016. Structure of government [online]: Available from canada.ca/en/government/system/structure.html.

Government of Canada. n.d. Recalls and safety alerts [online]: Available from healthycanadians.gc.ca/recall-alert-rappel-avis/index-eng.php?_ga=1.68488849.1802858674.1490987709.

Government of Newfoundland and Labrador. 2004. OxyContin task force final report [online]: Available from health.gov.nl.ca/health/publications/oxycontin_final_report.pdf.

Guarner F, Sanders ME, Gibson G, Klaenhammer T, Cabana M, Scott K, et al. 2011. Probiotic and prebiotic claims in Europe: seeking a clear roadmap. British Journal of Nutrition, 106(11): 1765–1767. PMID: 21736772 DOI: 10.1017/S0007114511002248

Guindon GE, and Contoyannis P. 2012. A second look at pharmaceutical spending as determinants of health outcomes in Canada. Health Economics, 21: 1477–1495. PMID: 18972325 DOI: 10.1002/hec.1415

Haiser HJ, Gootenberg DB, Chatman K, Sirasani G, Balskus EP, and Turnbaugh PJ. 2013. Predicting and manipulating cardiac drug inactivation by the human gut bacterium *Eggerthella lenta*. Science, 341: 295–298. PMID: 23869020 DOI: 10.1126/science.1235872

Hayden EC. 2014. Misleading mouse studies waste medical resources. Retrospective of more than 100 failed drugs show many should have never made it to clinical trials. Nature News [online]: Available from nature.com/news/misleading-mouse-studies-waste-medical-resources-1.14938.

Health Canada. 2007a. Brief history of drug regulation in Canada [online]: Available from hc-sc.gc.ca/dhp-mps/homologation-licensing/info-renseign/hist-eng.php.

Health Canada. 2007b. Drugs and health products: drug licensing process [online]: Available from hc-sc.gc.ca/dhp-mps/homologation-licensing/system/map-carte/index-eng.php.

Health Canada. 2007c. Health Products and Food Branch (HPFB)-Roadmap for 2007–2012 [online]: Available from hc-sc.gc.ca/ahc-asc/pubs/hpfb-dgpsa/map-feuille-2007-2012-eng.php.

Health Canada. 2009a. Blueprint for renewal: transforming Canada's approach to regulating health products and food [online]: Available from hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/blueprint-plan/index-eng.php.

Health Canada. 2009b. Managing health claims for foods in Canada: towards a Modernized Framework—2007 Health Canada consultation document [online]: Available from hc-sc.gc.ca/fn-an/consult/_man-gest_health_claims-allegations_sante/index-eng.php.

Health Canada. 2009c. Guidance document for preparing a submission for food health claims [online]: Available from hc-sc.gc.ca/fn-an/legislation/guide-ld/health-claims_guidance-orientation_allegations-sante-eng.php.

Health Canada. 2009d. Guidance document—the use of probiotic microorganisms in food [online]: Available from hc-sc.gc.ca/fn-an/legislation/guide-ld/probiotics_guidance-orientation_probiotiques-eng.php.

Health Canada. 2010. Drugs and health products: introduction to the current system [online]: Available from hc-sc.gc.ca/dhp-mps/homologation-licensing/system/intro-eng.php.

Health Canada. 2011a. Guidance document for preparing a submission for food health claims [online]: Available from hc-sc.gc.ca/fn-an/legislation/guide-ld/health-claims_guidance-orientation_allegations-sante-eng.php.

Health Canada. 2011b. Drugs and health products: regulations of health products advertising in Canada—overview for physicians [online]: Available from hc-sc.gc.ca/dhp-mps/advert-publicit/pol/overview-apercu-eng.php.

Health Canada. 2012. Guidance for industry—priority review of drug submissions [online]: Available from hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/priorit/priordr-eng.php.

Health Canada. 2017a. Consultation on the regulation of self-care products. canada.ca/en/health-canada/programs/consultation-regulation-self-care-products.html.

Health Canada. 2017b. About Health Canada: branches and agencies [online]: Available from hc-sc.gc.ca/ahc-asc/branch-dirgen/index-eng.php.

Health Canada. 2017c. Listing of monographs [online]: Available from webprod.hc-sc.gc.ca/nhpid-bdipsn/monosReq.do?lang=eng&monotype=single.

Health Canada. 2017d. Health claim assessments [online]: Available from hc-sc.gc.ca/fn-an/label-etiquet/claims-reclam/assess-evalu/index-eng.php#fnb3.

Hobbs JE, Malla S, and Sogah EK. 2014. Regulatory frameworks for functional food and supplements. Canadian Journal of Agricultural Economics, 62: 569–594. DOI: 10.1111/cjag.12051

Hollis A, and Ibbott P. 2006. How parallel trade affects drug policies and prices in Canada and the United States. American Journal of Law & Medicine, 32(2–3): 193–217. PMID: 16927610 DOI: 10.1177/009885880603200204

Jepson GS. 2002. Regulation of natural health products in Canada. Food and Drug Law Journal, 57(1): 59–71. PMID: 12118481

Jernberg C, Löfmark S, Edlund C, and Jansson JK. 2010. Long-term impacts of antibiotic exposure on the human intestinal microbiota. Microbiology, 156(11): 3216–3223. PMID: 20705661 DOI: 10.1099/mic.0.040618-0

Khan S, Knapp CW, and Beattie TK. 2016. Antibiotic resistant bacteria found in municipal drinking water. Environmental Processes, 3: 541–552. DOI: 10.1007/s40710-016-0149-z

Kim H. 2015. Trouble spots in online direct-to-consumer prescription drug promotion: a content analysis of FDA warning letters. International Journal of Health Policy and Management, 4(12): 813–821. PMID: 26673465 DOI: 10.15171/ijhpm.2015.157

Kitazawa H, Alvarez S, Suvorov A, Melnikov V, Villena J, and Sánchez B. 2015. Recent advances and future perspective in microbiota and probiotics. BioMed Research International, 2015: 275631. PMID: 25984528 DOI: 10.1155/2015/275631

Kondro W. 2000. Canada overhauls food and drug regulations. The Lancet, 355(9214): 1527. DOI: 10.1016/S0140-6736(05)74587-6

Law MR. 2014. The characteristics and fulfillment of conditional prescription drug approvals in Canada. Health Policy, 116(2–3): 154–161. PMID: 24703857 DOI: 10.1016/j.healthpol.2014.03.003

Lexchin J. 2007. Notice of compliance with conditions: a policy in limbo. Healthcare Policy, 2(4): 114–122. PMID: 19305737

Lexchin J. 2010. Drug safety and Health Canada. International Journal of Risk & Safety in Medicine, 22(1): 41–53. DOI: 10.3233/JRS-2010-0490

Lexchin J, and Gleeson D. 2016. The Trans Pacific Partnership Agreement and pharmaceutical regulation in Canada and Australia. International Journal of Health Services, 46(4): 597–613. PMID: 27516183 DOI: 10.1177/0020731416662612

Lexchin J, and Kohler JC. 2011. The danger of imperfect regulation: OxyContin use in the United States and Canada. International Journal of Risk & Safety in Medicine, 23: 233–240. PMID: 22156088 DOI: 10.3233/JRS-2011-0539

Lexchin J, Wiktorowicz M, Moscou K, and Eggertson L. 2013. Provincial drug plan officials' views of the Canadian drug safety system. Journal of Health Politics, Policy and Law, 38(3): 545–571. PMID: 23418364 DOI: 10.1215/03616878-2079514

Light DW, Lexchin J, and Darrow JJ. 2013. Institutional corruption of pharmaceuticals and the myth of safe and effective drugs. The Journal of Law, Medicine & Ethics, 41(3): 590–600. PMID: 24088149 DOI: 10.1111/jlme.12068

Lurie P, and Wolfe SM. 2005. Misleading data analyses in salmeterol (SMART) study. The Lancet, 366(9493): 1261–1262. PMID: 16214589 DOI: 10.1016/S0140-6736(05)67518-6

MacKinnon JIJ. 2016. Tighter regulations needed for over-the-counter codeine in Canada. Canadian Pharmacists Journal, 149(6): 322–324. PMID: 27829853 DOI: 10.1177/1715163516660572

Martinez RCR, Franceschini SA, Patta MC, Quintana SM, Gomes BC, De Martinis EC, et al. 2009a. Improved cure of bacterial vaginosis with single dose of tinidazole (2 g) and *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14: a randomized, double-blind, placebo-controlled trial. Canadian Journal of Microbiology, 55(2): 133–138. PMID: 19295645 DOI: 10.1139/W08-102

Martinez RCR, Franceschini SA, Patta MC, Quintana SM, Candido RC, Ferreira JC, et al. 2009b. Improved treatment of vulvovaginal candidiasis with fluconazole plus probiotic *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14. Letters in Applied Microbiology, 48(3): 269–274. PMID: 19187507 DOI: 10.1111/j.1472-765X.2008.02477.x

Mintzes B, Lexchin J, Sutherland JM, Beaulieu MD, Wilkes MS, Durrieu G, et al. 2013. Pharmaceutical sales representatives and patient safety: a comparative prospective study of information quality in Canada, France and the United States. Journal of General Internal Medicine, 28(10): 1368–1375. PMID: 23558775 DOI: 10.1007/s11606-013-2411-7

Natural Health Products Regulations. 2003. SOR, 2003-196 [online]: Available from laws-lois.justice.gc.ca/eng/regulations/SOR-2003-196/.

Nestmann ER, Harwood M, and Martyres S. 2006. An innovative model for regulating supplement products: natural health products in Canada. Toxicology, 221(1): 50–58. PMID: 16472903 DOI: 10.1016/j.tox.2006.01.013

Office of Natural Health Products (Canada). 2000. A fresh start: final report of the ONHP Transition Team [online]: Available from torontopubliclibrary.ca/detail.jsp?Entt=RDM1933491&R=1933491.

Parliament of Canada. 1998. Natural health products: a new vision report of the standing committee on health [online]: Available from parl.gc.ca/HousePublications/Publication.aspx?DocId=1031528.

Pew Health Group. 2011. After heparin: protecting consumers from the risks of substandard and counterfeit drugs [online]: Available from pewtrusts.org/~/media/legacy/uploadedfiles/wwwpewtrustsorg/reports/health/pewheparinfinalhrpdf.pdf.

Rapoport D. 2005. Perspective on drug withdrawals. Canadian Medical Association Journal, 173(2): 128–129. PMID: 16027414 DOI: 10.1503/cmaj.1050016

Rawson NSB. 2002. Human resources for the approval of new drugs in Canada, Australia, Sweden, the United Kingdom and the United States. The Canadian Journal of Clinical Pharmacology, 9(2): 73–78. PMID: 12172587

Rawson NSB. 2015. Health Canada's use of priority review status for drugs for unmet needs. Regulatory Toxicology and Pharmacology, 73(1): 391–395. PMID: 26260656 DOI: 10.1016/j.yrtph.2015.08.002

Sanders ME. 2003. Probiotics: considerations for human health. Nutrition Reviews, 61(3): 91–99. PMID: 12723641 DOI: 10.1301/nr.2003.marr.91-99

Sanders ME, and Levy DD. 2011. The science and regulations of probiotic food and supplement product labeling. Annals of the New York Academy of Sciences, 1219(Suppl. 1): E1–E23. PMID: 21332758 DOI: 10.1111/j.1749-6632.2010.05956.x

Sanders ME, Lenoir-Wijnkoop I, Salminen S, Merenstein DJ, Gibson GR, Petschow BW, et al. 2014. Probiotics and prebiotics: prospects for public health and nutritional recommendations. Annals of the New York Academy of Sciences, 1309(1): 19–29. PMID: 24571254 DOI: 10.1111/nyas.12377

Sanders ME, Shane AL, and Merenstein DJ. 2016. Advancing probiotic research in humans in the United States: challenges and strategies. Gut Microbes, 7(2): 97–100. PMID: 26963522 DOI: 10.1080/19490976.2016.1138198

Shajarizadeh A, and Hollis A. 2015a. Delays in the submission of new drugs in Canada. Canadian Medical Association Journal, 187(1): E47–E51. PMID: 24821865 DOI: 10.1503/cmaj.130814

Shajarizadeh A, and Hollis A. 2015b. Price-cap regulation, uncertainty and the price evolution of new pharmaceuticals. Health Economics, 24: 966–977. PMID: 24990225 DOI: 10.1002/hec.3075

Shanks N, Greek R, and Greek J. 2009. Are animal models predictive for humans? Philosophy Ethics Humanities in Medicine, 4:2. PMID: 19146696 DOI: 10.1186/1747-5341-4-2

Sibbald B. 2004. Rofecoxib (Vioxx) voluntarily withdrawn from market. Canadian Medical Association Journal, 171(9): 1027–1028. PMID: 15505253 DOI: 10.1503/cmaj.1041606

Silversides A. 2010. Drug safety provisions in US and Europe outshine Canada. Canadian Medical Association Journal, 182(1): E23–E24. PMID: 19901046 DOI: 10.1503/cmaj.109-3102

Skokovic-Sunjic D. 2016. Clinical guide to probiotic products [online]: Available from probioticchart.ca.

Smith A, Jogalekar S, and Gibson A. 2014. Regulation of natural health products in Canada. Journal of Ethnopharmacology, 158(Part B): 507–510. PMID: 24969823 DOI: 10.1016/j.jep.2014.06.037

Spanogiannopoulos P, Bess EN, Carmody RN, and Turnbaugh PJ. 2016. The microbial pharmacists within us: a metagenomic view of xenobiotic metabolism. Nature Reviews Microbiology, 14: 273–287. PMID: 26972811 DOI: 10.1038/nrmicro.2016.17

Stanbrook MB, and Killeen RM. 2012. Canada falls short on safeguarding its drug supply. Canadian Medical Association Journal, 184(13): 1449–1449. PMID: 22908148 DOI: 10.1503/cmaj.121196

Suez J, Korem T, Zilberman-Schapira G, Segal E, and Elinav E. 2015. Non-caloric artificial sweeteners and the microbiome: findings and challenges. Gut Microbes, 6(2): 149–155. PMID: 25831243 DOI: 10.1080/19490976.2015.1017700

Vandergrift M, and Kanavos P. 1997. Health policy versus industrial policy in the pharmaceutical sector: the case of Canada. Health Policy, 41(3): 241–260. PMID: 10170092 DOI: 10.1016/S0168-8510(97)00036-5

Wegener HC. 2003. Antibiotics in animal feed and their role in resistance development. Current Opinion in Microbiology, 6(5): 439–445. PMID: 14572534 DOI: 10.1016/j.mib.2003.09.009

Wiktorowicz ME. 2003. Emergent patterns in the regulation of pharmaceuticals: institutions and interests in the United States, Canada, Britain, and France. Journal of Health Politics, Policy and Law, 28(4): 615–658. DOI: 10.1215/03616878-28-4-615

Wood AJJ. 2006. A proposal for radical changes in the drug-approval process. The New England Journal of Medicine, 355(6): 618–623. PMID: 16899784 DOI: 10.1056/NEJMsb055203

Yallapragada SG, Nash CB, and Robinson DT. 2015. Early-life exposure to antibiotics, alterations in the intestinal microbiome, and risk of metabolic disease in children and adults. Pediatric Annals, 44(11): e265–e269. PMID: 26587819 DOI: 10.3928/00904481-20151112-09

Yeates N, Lee DK, and Maher M. 2007. Health Canada's progressive licensing framework. Canadian Medical Association Journal, 176(13): 1845–1847. PMID: 17576983 DOI: 10.1503/cmaj.070597