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Article abstract

Drug regulatory bodies aim to ensure that patients have access to safe and effective drugs; however, no matter the quality of pre-licensure studies, uncertainty will remain regarding the safety and effectiveness of newly approved drugs until a large and diverse population uses those drugs. Recent analyses of Canada's post-market drug surveillance (PMDS) system have found that Canada's PMDS system requires strengthening and that efforts must be improved to monitor and address the safety and effectiveness of approved drugs among vulnerable populations. Given the uncertainty that exists when drugs enter the market, some have suggested that the precautionary principle is relevant to guiding decision-making in this context. This paper responds to recommendations that the Canadian PMDS system should be responsive to the health needs of vulnerable populations by assessing the utility of deploying the precautionary principle to guide a post-market strategy for vulnerable populations.

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ARTICLE (ÉVALUÉ PAR LES PAIRS / PEER-REVIEWED)

Deploying the Precautionary Principle to Protect Vulnerable Populations in Canadian Post-Market Drug Surveillance

Maxwell J. Smith^a, Ana Komparic^b, Alison Thompson^b

Résumé

Les organismes de réglementation des médicaments visent à garantir que les patients aient accès à des médicaments sûrs et efficaces. Toutefois, quelle que soit la qualité des études préalables à l'autorisation de mise sur le marché, l'incertitude subsistera quant à la sécurité et à l'efficacité des médicaments nouvellement approuvés tant qu'une population nombreuse et diversifiée n'utilisera pas ces médicaments. Des analyses récentes du système canadien de surveillance des médicaments après leur mise sur le marché (PMDS) ont révélé que le PMDS du Canada doit être renforcé et que les efforts doivent être améliorés pour surveiller et traiter la sécurité et l'efficacité des médicaments approuvés parmi les populations vulnérables. Étant donné l'incertitude qui règne lorsque les médicaments entrent sur le marché, certains ont suggéré que le principe de précaution est pertinent pour guider la prise de décision dans ce contexte. Ce document répond aux recommandations selon lesquelles le système canadien de surveillance des médicaments après leur mise sur le marché devrait répondre aux besoins de santé des populations vulnérables en évaluant l'utilité de déployer le principe de précaution pour guider une stratégie post-commercialisation pour les populations vulnérables.

Mots-clés

principe de précaution, incertitude, populations vulnérables, surveillance des médicaments après leur mise sur le marché, réglementation pharmaceutique

Abstract

Drug regulatory bodies aim to ensure that patients have access to safe and effective drugs; however, no matter the quality of pre-licensure studies, uncertainty will remain regarding the safety and effectiveness of newly approved drugs until a large and diverse population uses those drugs. Recent analyses of Canada's post-market drug surveillance (PMDS) system have found that Canada's PMDS system requires strengthening and that efforts must be improved to monitor and address the safety and effectiveness of approved drugs among vulnerable populations. Given the uncertainty that exists when drugs enter the market, some have suggested that the precautionary principle is relevant to guiding decision-making in this context. This paper responds to recommendations that the Canadian PMDS system should be responsive to the health needs of vulnerable populations by assessing the utility of deploying the precautionary principle to guide a post-market strategy for vulnerable populations.

Keywords

precautionary principle, uncertainty, vulnerable populations, postmarket drug surveillance, pharmaceutical regulation

Introduction

An expansive literature exists that concerns itself with the principles and values that ought to govern the research, development, and oversight of pre-licensure pharmaceuticals, particularly with respect to how human participants and vulnerable populations ought to be treated (1-4). Reflecting movements to adopt a life-cycle approach to drug regulation (5), interest is now increasingly turning toward assessing the appropriate mechanisms that ought to guide the surveillance, evaluation, and regulatory management of pharmaceuticals once they have been approved and licensed for public consumption (hereafter understood as 'post-market surveillance').

Yet, the attention paid thus far to the welfare of vulnerable populations in Canadian post-market surveillance has been surprisingly asymmetrical relative to pre-licensure drug research. This is problematic because certain vulnerable populations may be at increased risk of suffering adverse reactions from newly approved drugs or may require special consideration for increased protection due to systematic disadvantage. This paper therefore seeks to analyze how the interests and welfare of vulnerable populations might be better incorporated into Canadian post-market drug surveillance.¹ In particular, given the uncertainty that exists when drugs enter the market, this paper examines the prospect of adopting the precautionary principle as a guide to decision-making to achieve this aim – a principle that is increasingly cited in drug safety (6-8) and which emphasizes that precautionary measures should be taken when an activity raises threats of harm, even when cause and effect relationships between that activity and harm are not fully established. We proceed by providing a brief description of Canada's post-market surveillance system, discuss what we mean by 'vulnerable populations' and the 'precautionary principle', and then examine whether and how the precautionary principle might be deployed to protect vulnerable populations from harm in this context.

Post-Market Surveillance of Drugs in Canada

Historically, a significant number of drugs have been found to have serious health concerns only *following* approval for public use. For instance, 23.7% of drugs examined between 1995 and 2010 demonstrated a serious safety issue post-approval in Canada (9). Post-market surveillance is a systematic mechanism to monitor, assess, manage, and report on these issues.

¹ This paper is concerned chiefly with post-market surveillance as it applies to drugs, and not necessarily to biologics or vaccines. This is not to say, however, that the analysis cannot be similarly considered in light of health products other than drugs.

Once drugs receive market approval from Health Canada, the Marketed Health Products Directorate (MHPD) within Health Canada's Health Products and Food Branch (HPFB) conducts monitoring. Operated by the Canada Vigilance Program, reports of suspected adverse drug reactions submitted by health professionals, drug manufacturers, and consumers both domestically and internationally are collected and subsequently analyzed for risk signals and safety trends. Signal detection involves a "preliminary indication of a product-related safety issue," where "assessment consists of the scientific/medical review of multiple data sources to analyse risks and benefits, while determining the likelihood of the association between the reaction and the health product" (10). Once risks are identified, Health Canada may then choose to initiate a risk management approach, which may include the communication of risk to health professionals and the public, labelling changes including black box warnings, and recommending the removal of a product from the market. In order to determine which action to take in the presence of a risk signal, Health Canada applies a risk-based approach that prioritizes safety issues and conducts an analysis to determine whether any further action is required.

In a move to increase capacity for active surveillance of post-approval drugs, the Drug Safety and Effectiveness Network (DSEN) was created in 2009 within the Canadian Institutes of Health Research (CIHR), which is at arm's length from Health Canada. DSEN is tasked with carrying out post-approval studies in response to potential safety signals of authorized pharmaceuticals identified by Health Canada, with the objective of generating evidence to support policy decisions at the federal and provincial/territorial levels. DSEN responds to requests for more information from regulators, health technology assessors, drug plan managers, and policymakers. Some of the research DSEN has funded, for instance, has found high-potency statin drugs causing acute kidney injury, but the Network's overall effectiveness has been questioned, largely due to insufficient funding (11). CIHR's Strategy for Patient-oriented Research (SPOR) also contributes to post-market surveillance in Canada through funding investigator-initiated research (12).

Despite these initiatives, analyses of Canadian post-market surveillance activities published within the past decade have argued that Canada's post-market surveillance system requires strengthening, and in particular, have noted that efforts must be improved to monitor and address the safety and effectiveness of approved drugs among population subgroups, such as children, pregnant women, the elderly, and First Nations, Métis, and Inuit populations. For instance, a 2011 Report by the Auditor General of Canada on the regulation of pharmaceutical drugs noted that Health Canada had not implemented a strategy for monitoring adverse drug reaction reports from vulnerable populations (13) – something that was also labelled an 'issue of concern' in a 2013 Report on post-market drug safety and effectiveness surveillance by the Canadian Standing Senate Committee on Social Affairs, Science and Technology (12, p.7). Overall, it has been noted that the adverse drug reaction reports submitted to Health Canada represent less than 10% of the actual total, with others noting that this number may more likely be less than 5% (12-13). In the absence of significant system overhaul and improvement in reporting rates, a different approach for risk-benefit analysis and risk communication about potentially harmful drugs may be warranted.

While the need to strengthen post-market surveillance for vulnerable populations has been recognized in Canada, there has been limited discussion of what it requires in practice, and in particular, when and on what grounds different approaches to post-market surveillance may be justified. For example, the Senate Report offered 19 recommendations to strengthen post-market pharmaceutical safety and effectiveness surveillance in Canada, including calling for greater investment into post-market surveillance and granting Health Canada greater regulatory authority for requesting post-market surveillance studies and making labelling changes for marketed drugs (12). Furthermore, in recognition of the need to collect post-market data from population subgroups, recommendation 12 called for "the implementation of a post-approval strategy for drug manufacturers and/or the Drug Safety and Effectiveness Network to conduct studies of new drugs in relevant sub-groups of the population." (12, p.23) The Report also specifically recommended that a modernized drug regulatory framework include "systematic safety reviews of drugs used in the paediatric population." (12, p.24) Nonetheless, the Report provided little guidance with respect to criteria for determining an appropriate or ethically justifiable post-market surveillance strategy for vulnerable populations. Our analysis of the precautionary principle and its component features and implications highlights normative considerations relevant to the development of strategies aimed at improving the safety and effectiveness of drugs used by members of vulnerable populations.

On 'Vulnerable Populations'

A prerequisite for developing a specific post-approval strategy for 'vulnerable populations' or 'relevant population subgroups' is the ability to identify and characterize such groups. Other than identifying categorical examples of groups traditionally considered to be vulnerable by virtue of their routine exclusion from clinical trials (e.g., 'children,' 'the elderly'), the aforementioned reports do little to characterize which other population subgroups may be relevant, or specify the criteria through which such subgroups ought to be identified. A post-approval surveillance strategy for vulnerable populations will require some specificity if it is to meaningfully and consistently identify those groups for whom it is supposed to be concerned.

A significant literature has devoted itself to the analysis of what constitutes 'vulnerability' and 'vulnerable populations.' It is beyond the scope of this paper to reflect on what this could, or ought to, mean in any robust manner. However, it is worth noting that some population subgroups could be considered vulnerable *a priori* by virtue of their exclusion from pre-licensure clinical trials. As such, special attention – whatever that means at this point – in surveillance and risk management activities could be paid to those groups who have been excluded from the pre-licensure studies. Even if included in clinical trials, though,

some population subgroups may prove vulnerable for other reasons, due to genetic, biological, behavioural, or social factors, and may therefore be worthy of special attention in post-market surveillance activities. Those populations who are at higher risk of morbidity and mortality due to age, genetic mutations, or physiological factors, for instance, may be one basis for special consideration. Focus exclusively on these biological considerations, though, may mean that vulnerabilities arising from systematic social, economic, and political marginalization and disadvantage will be altogether missed. For instance, how certain populations are socially and economically situated may affect their capability to access drugs or comply with drug regimens, thus exposing them to risks related to lessened effectiveness or even safety risks (14-15). The exclusion of social vulnerability in the assessment of effectiveness and safety among population subgroups in post-market surveillance in favour of the (sole) consideration of biological vulnerability could therefore lead to the omission of vulnerabilities that result from relevant social determinants of health and thereby fail to protect some vulnerable groups who might require enhanced surveillance and preventative health interventions.

Unfortunately, there is no way of knowing with complete certainty which groups will be most vulnerable to adverse drug reactions or harm resulting from diminished drug effectiveness. The use of population categories traditionally considered to be at risk (which justify their exclusion from pre-market clinical trials) – such as pregnant women, nursing women, children, and the elderly – is one approach. However, using such an approach for the real-world context may tend to include individuals or populations typically considered at risk, when in reality they are not at risk, and exclude those that actually are at risk (and, again, neglect those who may be socially vulnerable for other reasons) (16). Relying on fixed, predetermined categories of (predominantly biological) vulnerability may neglect contextual factors that will be necessary to remediate if population subgroups are to be adequately protected from harm. Engaging with communities that are expected to use particular drugs may be one strategy to reveal important information about how surveillance and risk management interventions ought to be conducted, as communities may be aware of their unique (biological and social) vulnerabilities (17). As will become apparent in the following section, this strategy would be aligned with the Government of Canada's *Framework for the Application of Precaution in Science-Based Decision-Making about Risk*, which asserts that decisions guided by the public's chosen level of protection against risk ought to be considered legitimate (18). Ultimately, a community's chosen level of protection against risk will be intimately linked with that community's understanding and awareness of their own vulnerabilities.

Precautionary Principle

The precautionary principle is derived from environmental risk management policy and has more recently been applied to public health decision-making (19-21). There is no consensus definition or interpretation – legal or otherwise – of the precautionary principle in either environmental or public health policy. Two oft-cited definitions are provided here in order to develop an understanding of the core elements of the principle.

Rio Declaration on Environment and Development

Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation (United Nations, 1992) (22).

The Wingspread Consensus Statement on the Precautionary Principle

When an activity raises threats of harm to the environment or human health, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically. In this context the proponent of an activity, rather than the public, bears the burden of proof (Wingspread Conference Participants, 1998) (23).

Key elements present in both formulations of the precautionary principle, and most others, include the potential for an irreversible or serious harm to health, the need to make a decision or take preventive and/or anticipatory action, and a lack of scientific certainty. Formulations like the Wingspread Statement also include exploring a wide range of alternatives to the potentially harmful actions, increasing participation from the public in decision-making, and shifting the burden of proof of a cause and effect relationship from the public (e.g., a decision-maker) to the proponent of the activity or product. In short, the precautionary principle advances that, in situations where risk of serious or irreversible harm exists, a greater level of uncertainty shall not be a reason for policymakers not to take action to protect against that risk. Precautionary reasoning may be viewed as a recognition that acting under conditions of scientific uncertainty relies on the distinctly political process of determining an 'acceptable' level of risk (24).

Stephen John distinguishes between two common motivations behind the precautionary principle (25). On the one hand, the precautionary principle may be interpreted as suggesting a lowering of the epistemic standards used to appraise evidence in a certain class of outcomes that are, or ought to be, viewed as special (e.g., on account of their severity or irreversible nature or due to the fact that they occur among particular population groups), and accordingly cannot be assessed solely through standard means of appraisal, such as traditional risk-benefit analysis. Conversely, the precautionary principle may be interpreted as suggesting a duty-based recognition of the wrongness of different types of risks (e.g., risks to the health of vulnerable populations).

The precautionary principle can be formulated in its strong or weak form. The strong form, which is reflected in the Wingspread Statement, claims that regulation is required *whenever* a risk of harm to health exists *even if* evidence supporting the existence of such a risk is speculative. The strong formulation usually does not consider the costs associated with applying the principle. The weak form, on the other hand, merely proposes that precautionary action not be precluded simply due to a lack of evidence, particularly if the consequences of not taking action would be serious and irreversible. Here, benefits of precautionary action may be weighed against its associated costs (26).

The precautionary principle has been adopted in numerous international treaties, legislations, and policies. Debate about the relevance of the precautionary principle to post-market surveillance and pharmaceutical risk management in particular is still in its early stages; that is to say, the principle has been identified as having some relevance in this context but it is not yet clear whether, how, and when it ought to be used in decision-making within an improved post-market surveillance regulatory system (6-8,27-30). In Canada, there has been a long history of applying precaution in federal regulatory decision-making about risk (18). Advocating for an approach aligned with the precautionary principle is not a novel idea in public health, either. Indeed, two Canadian judicial inquiries, the Krever Commission of Inquiry on the Blood System in Canada and the Campbell Commission following the outbreak of Severe Acute Respiratory Syndrome (SARS), recommend the use of the precautionary principle to guide Canada's response to public health threats (31-32). Additionally, Health Canada identifies using a precautionary approach as one of its three guiding principles in the Health Canada *Decision-Making Framework for Identifying, Assessing, and Managing Health Risks*, and released a framework in 2003 to guide the application of precaution in science-based decision making about risk in areas of federal regulatory activity for the protection of health and safety (33). The latter framework, hereafter referred to as the 'Canadian Framework,' describes 10 guiding principles that are meant to achieve the "coherent and cohesive application of precaution" in federal decision-making in contexts of uncertainty, which are outlined in Table A.

Table A: Government of Canada (2003) principles for the application of precaution in science-based decision making about risk

- | |
|--|
| <ol style="list-style-type: none"> 1. The application of precaution is a legitimate and distinctive decision-making approach within risk management. 2. It is legitimate that decisions be guided by society's chosen level of protection against risk. 3. Sound scientific information and its evaluation must be the basis for applying precaution; the scientific information base and responsibility for producing it may shift as knowledge evolves. 4. Mechanisms should exist for re-evaluating the basis for decisions and for providing a transparent process for further consideration. 5. A high degree of transparency, clear accountability and meaningful public involvement are appropriate. 6. Precautionary measures should be subject to reconsideration, on the basis of the evolution of science, technology and society's chosen level of protection. 7. Precautionary measures should be proportional to the potential severity of the risk being addressed and to society's chosen level of protection. 8. Precautionary measures should be non-discriminatory and consistent with measures taken in similar circumstances. 9. Precautionary measures should be cost-effective, with the goal of generating (i) an overall net benefit for society at least cost, and (ii) efficiency in the choice of measures. 10. Where more than one option reasonably meets the above characteristics, then the least trade-restrictive measure should be applied (p. 6-13). |
|--|

Source (36, p.13)

A significant literature now exists that seeks to clarify or modify the directives of the precautionary principle, and an equally significant literature exists seeking to critique the principle on several grounds.² While certainly relevant to the broader discussion, it is beyond the scope of this paper to incorporate either a defence of the principle or advocate for a particular interpretation of the principle that ought to be employed. Rather, the purpose of this paper is perhaps more practical: to apply a common interpretation of the precautionary principle to the context of post-market surveillance in Canada with special attention given to the guidance provided by the Government of Canada Framework in its assessment of the precautionary principle as a guide for a post-market strategy for vulnerable populations. While the analysis that follows could no doubt be challenged according to several criticisms of the precautionary principle itself (and these are welcomed, as this can only help advance the discussion), it warrants consideration in this context if not only because the precautionary principle will inevitably be considered relevant by policy-makers and decision-makers in this context because (a) the Government of Canada acknowledges the importance of the precautionary principle in federal decision-making about risk, and (b) the precautionary principle appears to be of *prima facie* relevance in post-market surveillance due to the inherent context of uncertainty and the heightened uncertainty surrounding post-market drug safety and effectiveness among vulnerable populations.

² For example, the precautionary principle has been criticized as being internally inconsistent, vague, an obstacle to innovation, and conducive to paralyzing decision-making. Debate also exists as to whether the precautionary principle ought to be considered a principle at all. Many criticisms are outlined in (18).

Precautionary Principle, Post-Market Surveillance, and Vulnerable Populations

Protecting Vulnerable Populations from Harm

A core presumption of the precautionary principle is the importance of protecting the public good, or in this context, the public's health (28). This requires drug regulators to favour those measures that protect public health, even if evidence of a threat to the public's health has not been fully established. This contrasts with scenarios where activities or products are assumed to be safe until demonstrated otherwise. When a presumption exists that an approved drug is safe until concerns of safety emerge, patients, especially those for whom no previous safety information exists, are put at increased risk. Accordingly, if they are to protect the public from harm, drug regulators guided by the precautionary principle should not assume, based on pre-licensure clinical trial information and even market approval, that drugs are safe until proven to be dangerous (6). A post-market surveillance strategy guided by the precautionary principle would therefore aim to *avoid* potential harms before a more complete picture about the existence of those harms emerges.

One of the primary features of public health and, indeed, the precautionary principle, is taking preventive and/or anticipatory action to mitigate a serious or irreversible harm to the population's health. Of course, in order to be able to take such anticipatory action, information will be required about whether risk of harm exists, might exist, or might soon exist. This information, if not available from pre-licensure studies, is generated from surveillance activities, including post-market research. Thus, surveillance activities capable of informing decision-makers such that they are able to *anticipate* and *prevent* serious or irreversible harm to the population's health, and not simply react to such harms once they emerge, should be considered a requirement of a precautionary approach to post-market surveillance.³ This has significant implications for a post-market surveillance strategy for vulnerable populations. Because even less information about drug safety and effectiveness tends to be available for vulnerable populations following market approval, targeted, active surveillance may be necessary to generate the safety and effectiveness data required to trigger swift risk management interventions if diminished effectiveness or safety concerns obtain in those populations.⁴ By contrast, a traditional risk assessment paradigm may not warrant the proactive implementation of special measures to capture safety and effectiveness information for vulnerable populations, but rather await the emergence of safety signals within such populations through universal, passive surveillance before more targeted surveillance, post-market studies, or risk management measures are initiated.

Once signals of a drug's diminished effectiveness or safety emerge, the precautionary principle might also be instructive for the initiation of risk management measures. The determination of whether, and how, to intervene following a safety signal in post-market surveillance, if based on an examination of known causal relationships between a drug and a safety concern, may result in the affected population sustaining harm while enough data is collected to be able to infer a causal relationship, which would constitute a failure of the drug regulator to mitigate substantial harm to the public's health. By contrast, the precautionary principle permits the introduction of risk management measures to prevent harm to the public's health even in the absence of scientific certainty of a threat. For example, in the past Health Canada has issued warnings or other public advisories about potential safety concerns before a safety assessment was completed – an activity that seems aligned with this precautionary approach (12). This contrasts with a *reactive* approach that is more commonly taken by regulators through the use of passive adverse drug reaction reporting and the subsequent initiation of post-market studies.

In accordance with the presumption in favour of protecting the public's health, the precautionary principle may also militate against competing interests borne out of profit or other ends that may be of interest to the pharmaceutical industry, or in other words, "the putative ability of commercial producers to manipulate regulatory policies and decisions to their self-interested ends; either directly by exerting pressure on agency decision makers or indirectly through elected officials" (7, p.339). The worry is that drug regulatory policies and decisions may, at times, serve the interests of drug manufacturers rather than the public good due to industry influence on data collection and reporting (35). If these worries do indeed reflect reality, this ought to be troubling because the vast majority of safety and efficacy data resulting from pre-approval studies is generated from industry, and because industry may ultimately end up playing a greater role in post-market studies (35-36). There is all the more reason, then, to adopt a regulatory approach that is guided by a principle that has at its core a presumption in favour of protecting the public's health rather than acting in accordance with the presumption that a drug is safe until proven otherwise.

However, different degrees of protection may be required by the precautionary principle depending on whether it is understood in its weak or strong form. A weak formulation of the precautionary principle in this context would authorize, but not require, regulators to place constraints on the use of a drug that poses a threat to human health and allow regulators to balance risks and benefits when making that decision. Judgments could be made resulting in the acceptance of a given risk to health in virtue of a benefit or because it would be too costly to avoid. For instance, if safety signals emerge for a newly approved drug that addresses a serious, life-threatening, or severely debilitating disease or condition for which no alternative therapy exists, a weak precautionary approach may tolerate those risks in virtue of the benefits that may accrue from the drug and/or the harms that may be reasonably expected to result from initiating a risk management strategy (e.g., removing the drug from the market). On the other hand, if the comparative effectiveness of a newly approved drug is called into question as a result of

³ Furthermore, a precautionary approach may necessitate the inclusion of vulnerable populations in pre-licensure studies in order to generate pertinent information to protect vulnerable populations post-licensure.

⁴ Enhanced surveillance activities such as this have, for instance, been implemented within Canadian hospitals to actively monitor adverse events following immunization in paediatric populations (34). Similar surveillance activities do not exist, however, for other vulnerable populations or for other pharmaceutical products, like drugs.

post-market surveillance data, a weak precautionary approach may tolerate less exposure to risk, as a comparable therapy exists.

Alternatively, a strong formulation of the precautionary principle would require regulators to place constraints on a drug when a risk to human health is present regardless of potential benefits or costs of avoiding risk (7). A drug, therefore, may need to be removed from the market until it was demonstrated that it no longer posed the risk to health that caused it to be removed in the first place. An application of the precautionary principle in its strong form therefore raises important questions in this context about its unwillingness to permit the weighting of the relative benefits and harms that may accord to different populations. Two scenarios may emerge if strong precautionary action is taken: either safety signals will emerge from within vulnerable populations, resulting in the drug being removed from the market for further study (even if other 'non-vulnerable' populations may still benefit from the drug), or safety signals will emerge from within the general population, resulting in the drug being removed from the market for further study (even if vulnerable subpopulations may still benefit from the drug).⁵ Resolving what ought to be done in either case, it seems, would typically require some assessment of risks and benefits – something that is not countenanced by a strong formulation of the precautionary principle. This, it seems, could pose a problem for vulnerable populations. To avoid such aggressive actions but maintain special concern for vulnerable populations, other precautionary measures, like boxed warnings,⁶ could be utilized for those populations. As the Canadian Framework reminds us, a re-evaluation of decisions to take precautionary action may be triggered by the emergence of new information, such as evidence of harms that result from withdrawing a drug from the market, or from a change in society's risk tolerance [18]. Ultimately, the weighing of risks and benefits tolerated by such measures will be based on values and priorities, which requires input from those affected by such decisions in addition to the broader public.

Proportionality

Some claim that the principle of proportionality is intrinsic to the precautionary principle (8,37). This means that precautionary safety measures ought to be proportionate to the level and severity of risk to human health, or the public's chosen level of protection – something that may be achieved via broad and inclusive stakeholder engagement (18). Proportionate action required to protect the health of vulnerable populations in post-market surveillance may, *pro tanto*, require increased anticipatory safety measures (e.g., active surveillance) and more aggressive risk management for populations routinely excluded from pre-licensure clinical trials.

The implications of this are, for instance, that queries received by DSEN involving vulnerable populations ought to be prioritized for study, or that safety concerns ranked by Health Canada for review ought to be prioritized if they occur among populations considered to be vulnerable. Currently, both DSEN's prioritization of queries to study and Health Canada's ranking of safety concerns to review do not appear to take into account the population subgroups within which those safety concerns or queries originate (12). Another implication might be that more aggressive interventions, such as recommending removal of a drug from the market, would be more justifiable when safety signals are identified among vulnerable populations than when identified among other populations. At the moment, it may be difficult to justify the removal of a drug from the market if regulators require substantial evidence that a drug is the cause of a safety concern. Indeed, some have expressed concern about Health Canada's lack of authority to enforce the withdrawal of a drug after the emergence of safety concerns (38). The precautionary principle could be used to justify the issuance of authority to Health Canada to enforce the withdrawal of a drug from the market (or to issue a boxed warning) even when a causal relationship between the drug and a safety concern has not been fully scientifically established.

Lowering the Evidentiary Threshold

The precautionary principle involves the lowering of the epistemic standards necessary to justify the implementation of measures to protect the population from harm. If the evidentiary standard required to initiate a risk management intervention of any kind (e.g., further study of a drug, removal of a drug from the market) is too high, then the public's health may be threatened while waiting for that standard to be met. If the evidentiary standard required to initiate an intervention of any kind is too low, then the public may suffer unnecessary anxiety or fear, and drugs important for the health of the public may be under-accessed or not accessed at all. Thus, it is critically important to strike the right balance to determine what evidentiary standard ought to be required to initiate different regulatory interventions.

In its 2013 Report on post-market surveillance, the Canadian Standing Senate Committee on Social Affairs, Science and Technology emphasized that "there should not be a lower threshold of drug safety and effectiveness" for specific subgroups of the population, such as children, pregnant and nursing women, and the elderly (15, p.7). The Committee also asserted that "post-approval monitoring of prescription drugs must be strengthened in order to protect these subgroups" (p. viii), and suggested that this could be accomplished by including subgroups in pre-licensure clinical trials and by conducting post-approval studies and systematic safety reviews in relevant population subgroups. Finally, the Committee recommended that issues discovered by DSEN be considered for follow up studies.

⁵ The latter case, it seems, presents another sense in which such groups may be considered vulnerable.

⁶ A boxed warning is a warning included on a drug's box or package insert indicating that the drug may carry significant risk of serious or life-threatening adverse reactions.

The key difference between traditional risk-benefit assessments and risk management decisions under the rubric of the precautionary principle is that a lower evidentiary threshold exists to take precautionary measures in decision-making under the rubric of the precautionary principle. Thus, perhaps in strengthening post-market surveillance to protect vulnerable populations, there should be an *increased* threshold of drug safety and effectiveness. This means that drugs must be demonstrably *more* safe and effective if they are to be used among vulnerable populations. This would, perhaps, require a lowering not of drug safety and effectiveness, but rather a lowering of drug safety and effectiveness evidentiary thresholds required to initiate a risk management intervention. Furthermore, as previously mentioned, a precautionary approach may require enhanced surveillance as a mechanism of precaution in the first place – a mechanism that seeks to rectify evidentiary deficits about drug safety and effectiveness among vulnerable populations. This may be particularly relevant for drugs that receive approval through Health Canada's priority review system, where a shorter and arguably less stringent review process occurs for drugs that purport to address serious, life-threatening, or severely debilitating diseases or conditions.

Shifting the Burden of Proof

Perhaps the most significant insight that can be gleaned from the consideration of the precautionary principle in this context has to do with who bears the burden of proof to demonstrate drug safety and effectiveness in post-market surveillance. This burden of proof lies with the manufacturer when applying for regulatory approval. Once a drug is approved, however, this burden largely shifts from the manufacturer of the drug to the drug regulator. With that said, some proposals for post-market surveillance regulation consider giving drug regulators the authority to compel pharmaceutical manufacturers to undertake further post-market studies on safety and effectiveness (36).

Recall that the Wingspread Statement asserts that the "proponent of an activity, rather than the public, bears the burden of proof." In the context of a threat to population health, the 'activity' at hand can be considered a drug, or the licensure and distribution of a drug. And, it seems intuitive that, because the drug manufacturer has been responsible for the development and marketing of the drug, that they more justifiably ought to be considered the proponent of the activity.

As such, a reading of the Wingspread Statement's formulation of the precautionary principle suggests that, in the context of a threat to population health, the drug manufacturer rather than the drug regulator may bear the burden of proof for demonstrating safety and effectiveness when an activity raises threats of harm to human health. In the current regulatory environment this is not the case, as industry-sponsored phase IV trials are not required by Health Canada and queries stemming from safety signals or about diminished effectiveness require a response from Health Canada and DSEN, not the drug manufacturer.

However, there are reasons, namely concerns of credibility stemming from potential conflicts of interest, that could caution against drug manufacturers bearing the sole burden in demonstrating a drug's post-approval safety and effectiveness (39). This creates a potential challenge, as drug manufacturers and the pharmaceutical industry more generally may be in the best position to generate scientific data in a timely manner. Thus, innovative strategies involving collaborative arrangements among regulators, arms-length research and surveillance bodies, and drug manufacturers may be necessary in order to ensure the generation of scientific data is feasible, timely, and credible (18). As one option, to mitigate the spectre of conflicts of interest regulators could conduct (or fund) studies by third parties, or otherwise partner with third parties, to examine the safety of the drug.

Conclusion

Recent analyses of the Canadian post-market surveillance system have noted that efforts must be improved to monitor and address the safety and effectiveness of approved drugs among vulnerable populations. Consideration of how to identify and address the risks among vulnerable population within Canada's post-market surveillance system, and whether to adopt a precautionary approach in this setting, is critical given Canada's recent announcement that they are working to optimize the use of real-world evidence for drug regulatory decisions (40). While drug regulators involved in post-market surveillance must routinely operate in the context of uncertainty, heightened uncertainty about drug safety and effectiveness and, indeed, heightened risk exists for vulnerable populations. Given this heightened uncertainty and risk, the precautionary principle should be considered relevant to guiding decision-making in this context. Historically, the precautionary principle has arguably amplified the duties and powers of governments with respect to the protection of the environment (8). As such, it is similarly expected that, if applied in a post-market strategy for vulnerable populations, the precautionary principle may have the effect of amplifying duties and powers of drug regulators with respect to the protection of the health of society's most vulnerable populations.

Pre-licensure drug studies produce at least some evidence about safety and effectiveness that could inform many post-market surveillance and risk management activities for the general population. As such, a traditional risk-benefit approach may benefit a post-market surveillance strategy. The question, then, may not be whether and how the precautionary principle ought to figure in Canada's post-market surveillance system generally, but rather how it might be deployed in a post-market strategy to protect the health of vulnerable populations – populations for whom less evidence of safety and effectiveness tends to be available. Due to the increased uncertainty of risk and the enhanced potential for harm for vulnerable populations, a post-market strategy for vulnerable populations guided by the precautionary principle may be most appropriate to protect the health of those already disadvantaged. Without some consideration of the precautionary principle in this context, the post-market drug regulatory system in Canada could be considered unethical as it would place vulnerable Canadians at an unreasonably

heightened risk of exposure to drugs that may cause serious, though previously undetected, side-effects. Moreover, it would indicate a failure on the part of Health Canada to fulfil its mandate with respect to patient safety. The outstanding challenge in a precautionary approach, though, is to prevent the creation and/or exacerbation of vulnerability as a result of precautionary measures (e.g., from withdrawing a drug from the market). To better protect the health of vulnerable populations, the application of precaution from a post-market strategy ought to be guided by the unique health needs and awareness of community vulnerability that may exist among relevant population subgroups.

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Conflicts of Interest

None to declare

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