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Reforming the Regulation of Therapeutic Products in Canada: The Protecting of Canadians from Unsafe Drugs Act (Vanessa's Law)

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Abstract

Enacted November 2014, Vanessa's Law amends the *Food and Drugs Act* to give Health Canada greater powers to compel the disclosure of information, recall drugs and devices, impose fines and injunctions, and collect post-market safety information. The Act amends seriously outdated legislation that had been in place since 1954. While the explicit goals of the Act are to improve patient safety and provide transparency, it also establishes a regulatory framework that facilitates investment in the burgeoning field of biotechnology. While regulatory reform was already on the public agenda, public awareness of litigation against large pharmaceutical firms combined with the championing of the legislation by Conservative MP Terence Young, whose daughter Vanessa died from an adverse drug reaction, pushed the legislation through to implementation. Many key aspects of the Act depend upon the precise nature of supporting regulations that are still to be implemented. Despite the new powers conferred by the legislation on the Minister of Health, there is some concern that these discretionary powers may not be exercised, and that Health Canada may not have sufficient resources to take advantage of these new powers. Given experience to date since enactment, the new legislation, designed to provide greater transparency vis-à-vis therapeutic products, may actually have a chilling effect on independent scrutiny.

La Loi de Vanessa, qui a reçu la Sanction royale en novembre 2014, modifie la Loi sur les aliments et drogues *pour donner à Santé Canada plus de possibilités d'imposer la divulgation d'information, de retirer de la vente des médicaments et dispositifs, d'appliquer amendes et injonctions, et de collecter des informations sur la sécurité après la mise sur le marché. La Loi représente une modification en profondeur d'une législation surannée, en place depuis 1954. Si l'objectifs annoncé de la Loi sont d'améliorer la sécurité des patients et la transparence, elle établit aussi un cadre réglementaire facilitant l'investissement dans le domaine bourgeonnant des bio-technologies. Le besoin d'une réforme du cadre réglementaire se faisait déjà sentir, mais le passage de la Loi a été accéléré par la combinaison d'une sensibilisation du public aux actions en justice contre de grandes firmes pharmaceutiques et du parrainage de la législation par le député Conservateur Terence Young, dont la fille Vanessa est morte d'une réaction indésirable à un médicament. La Loi va dépendre crucialement de la nature précise des réglementations l'accompagnant, toujours en discussion. Malgré les nouveaux pouvoirs conférés par la Loi au Ministre de la santé, on peut craindre que ces pouvoirs discrétionnaires ne soient pas utilisés dans les faits et que Santé Canada manquent de ressources pour en tirer parti. En se fondant sur l'expérience depuis la Sanction royale, la nouvelle législation, bien que censée augmenter la transparence sur les produits thérapeutiques, pourrait en fait bloquer l'investigation indépendante.*

Key Messages

- Vanessa's Law gives Health Canada a much stronger legislative base from which to protect patient safety, but these powers remain largely discretionary.
- The new framework facilitates the post-market surveillance of therapeutic products.
- The precise mechanisms of serious adverse drug reporting will depend upon the formal implementation of the Draft Guidelines, the development of regulations supporting the legislation, and the construction of an effective framework permitting the systematic documentation of adverse events.

Messages-clés

- *La Loi de Vanessa confère à Santé Canada un arsenal législatif plus fourni pour protéger la sécurité des patients, mais l'utilisation de ces pouvoirs reste largement à la discrétion de l'Administration.*
- *Le nouveau cadre réglementaire rend plus facile la surveillance des produits thérapeutiques après leur mise sur le marché.*
- *Les mécanismes selon lesquels les effets indésirables graves seront enregistrés seront précisés lors de l'élaboration des projets de directives, du développement des règles de mise en œuvre de la législation, et de la mise en place d'un système de documentation effective des effets indésirables.*

1 BRIEF DESCRIPTION OF THE HEALTH POLICY REFORM

The *Protecting Canadians from Unsafe Drugs Act* (Vanessa's Law) was passed into law on 5 November 2014. This statute is an amendment to the *Food and Drugs Act*, and applies only to therapeutic drugs and medical devices (both of which are referred to as "therapeutic products"). It does not apply to natural health products, which are regulated under the National Health Products Regulations. Some of the new powers specified in Vanessa's Law came into force when the Act was passed; others will come into force when new regulations supporting the Act are adopted (see Table 1).

Table 1: Vanessa's Law: Current and Pending Provisions

Provisions in Force upon Royal Assent	Provisions Not in Force until Regulations Made
• Ability to compel information (21.1) • Ability to recall unsafe therapeutic products (21.3) • Ability to impose stronger fines and penalties (31, 31.2, 31.4) • Ability to incorporate by reference technical and non-technical documents into the Food and Drug Regulations (30.5) • Ability to disclose confidential business information (21.1) • Ability to direct label change / package modification (21.2) • Ability to seek injunction (21.5) • Obligation on the Minister of Health to make orders publicly available (21.4(2))	• Ability to require tests and studies (21.32) • Ability to order a reassessment (21.31) • Ability to attach terms and conditions to market authorizations (30(1.2)(b)) • Obligations on authorization holders to register clinical trials (21.71) and provide new safety information to the Minister (20(1.2)(d)) • Obligation on health care institutions to report serious drug reactions and medical device incidents to Health Canada (21.8) • Obligation on the Minister of Health to ensure that all positive and negative decisions, and the reasons for them, are publicly available (30(1.2)(b.1))

Source: (Government of Canada 2015)

The first set of powers gives the Minister of Health authority to compel information, including tests, studies, and reassessments. Under Vanessa's Law, if the Minister believes that a therapeutic product presents a serious risk of injury to human health, she may require that this information be provided to her (21.1.1). Subject to regulations, the Minister can order a drug manufacturer to conduct an assessment on a drug (21.31) or conduct tests,

studies, or observational studies related to the product (21.32). She may also disclose confidential business information without notification or consent if such risk exists (21.1.2). "Confidential business information" is defined in the Act (3.3) as "business information *a*) that is not publicly available, *b*) in respect of which the person has taken measures that are reasonable in the circumstances to ensure that it remains not publicly available, and *c*) that has actual or potential economic value to the person or their competitors because it is not publicly available and its disclosure would result in a material financial loss to the person or a material financial gain to their competitors."

This articulation of "confidential business information" is controversial because there is disagreement regarding whether the safety and effectiveness information supporting pharmaceuticals is "business" information that is properly subject to confidentiality, or whether it is "clinical" information that is essential to the creation of public knowledge supporting the protection of public health (Herder and Lemmens 2016, 3). The Minister now has clear authority to compel authorization holders to change the labeling on therapeutic products (21.2). Section 21.3 gives the Minister the power to recall a drug. While "recall" is not defined in the Act, it is understood by Health Canada as the "removal from further sale of use, or correction, of a distributed product that presents a risk to the health of consumers or violates legislation administered by the Health Products and Food Branch" (Health Canada 2012). Prior to the Act, drug recall was voluntary, and could not be enforced.

The Act also contains stricter enforcement provisions. Previously, the maximum fine that could be levied under the *Food and Drugs Act* was $5,000; under Vanessa's Law this has been increased to $5,000,000. Individuals can be subject to a two-year jail sentence (31.2). The Minister can now also order an injunction requiring anyone to refrain from committing an offence under the Act (such as continuing to sell a recalled drug).

A final set of powers and obligations focuses on disclosure. Subject to regulations, health care institutions will be required to report serious adverse drug reactions and medical device incidents (21.8). Those conducting clinical trials must register them, and make specific information public "within the prescribed time and in the prescribed manner" (21.71). The Minister, subject to regulations, has the power to impose terms and conditions on the authorizations given to those selling therapeutic products, and must make these terms and conditions publicly available. The Minister must ensure that all positive and negative decisions on the licensing of a product, and the reasons for them, are disclosed publicly. Drug makers must also disclose any information that they "receive or become aware of respecting the safety of the product," even if this information has its genesis outside of Canada (30.1.2).

2 HISTORY AND CONTEXT

The *Food and Drugs Act* was introduced in 1920, and significantly modified only once, in 1954. By 1998 there was much discussion within Health Canada regarding more substantial

reform in this area, but the effort failed due to a lack of political support (Jepson 2009). As part of the 10-Year Plan to Strengthen Health Care in 2004, First Ministers directed their respective health ministers to establish a Ministerial Task Force to develop and implement a National Pharmaceuticals Strategy, which included a focus on both pricing and purchasing strategies and real world drug safety and effectiveness. The task force presented a report in 2006, but there was little intergovernmental follow-up. However, Health Canada did proceed unilaterally in its attempt to update and consolidate laws focusing on the regulation of food, drugs, medical devices, cosmetics and natural health products.

In 2006 and 2007 Health Canada produced two complementary reports which together were referred to as the "Blueprint for Renewal." This was a very comprehensive reform project that introduced a lifecycle regulatory approach, greater regulatory transparency, and stricter compliance and enforcement provisions. On 8 April 2008, Bill C-51 (Proposed Amendments to the Food and Drugs Act) and Bill C-52 (Proposed Consumer Product Safety Act) were introduced in the House of Commons. The passage of Bill C-51 was delayed initially because of strong opposition from the natural health foods lobby, which objected to the more stringent regulations imposed upon natural health products. When an election was called in September 2008, Parliament was dissolved and both bills died on the order paper.

In November 2011, the Senate Standing Committee on Social Affairs, Science and Technology was authorized to examine and report on prescription pharmaceuticals in Canada. A series of four reports, focusing on clinical trials, post-approval monitoring, off-label use, and unintended consequences of drug use, were published between 2012 and 2014, with a final report issued in March 2015. The drafting of these early reports provided legislators with the background and context for Bill C-17, the *Protecting Canadians from Unsafe Drugs Act*, which was introduced in the House of Commons on 6 December 2013. The bill was referred to the Standing Committee on Health on 30 May 2014, after second reading in the House of Commons. There, in response to criticisms of the draft legislation presented by witnesses, the bill was amended to provide the Minister of Health greater discretion to disclose confidential business information (21.1 (2) and (3)); to require that the the Minister of Health make any such order for disclosure publicly available; to oblige drug manufacturers to ensure prescribed information is made public in a timely manner (21.71); and to provide Cabinet with the ability to make regulations on related matters (30 (1.2) (b.1), (c.1), (d.1), and (d.2)).[1] The bill passed through Senate without amendment on the 23 October 2014, and was given Royal Assent on 6 November 2014.

[1]The full set of amendments can be found in the Fifth Report of the Standing Committee of Health in the 41st Parliament, 2nd Session. The report is available online at: http://www.parl.gc.ca/HousePublications/Publication.aspx?Language=e&Mode=1&Parl=41&Ses=2&DocId=6664608

3 GOALS OF THE REFORM

The primary goal of Vanessa's Law was to modernize a highly outdated regulatory framework for pharmaceuticals. The articulated goals of the legislation, as outlined in the introductory summary of the Act, were to:

- strengthen safety oversight of therapeutic products throughout their life cycle,
- improve reporting by certain health care institutions of serious adverse drug reactions and medical device incidents that involve therapeutic products, and
- promote greater confidence in the oversight of therapeutic products by increasing transparency.

An implicit goal of the legislation was to provide a modern platform upon which to support an emergent biotechnology sector. A 2013 report by Industry Canada noted that the key growth area in pharmaceuticals was in "expensive specialty drugs" and "innovative/novel mechanisms" (Industry Canada 2013, 22). These niche drugs are increasingly focused upon genomic characteristics, which means that they can potentially target a very small number of individuals more effectively. But because of the limited numbers of people who can benefit from each drug, it is very difficult to enrol enough candidates to conduct a traditional randomized controlled trial. These drugs require a regulatory framework that allows the collection of post-market information on their safety and effectiveness, and facilitates faster entry of these drugs into the marketplace (see Appendix). Industry Canada encourages investment in "niche areas within biologics and oncology," and notes that "[d]ecisions and interpretations by Health Canada, the Patented Medicines Prices Review Board and provincial regulatory bodies affect the attractiveness of the Canadian market and consequently the investment decisions of global companies" (Industry Canada 2013, 26). The system of post-market surveillance established by Vanessa's Law thus provides the initial framework for investment in the lucrative field of biotechnology.

4 FACTORS THAT INFLUENCED HOW THE REFORM WAS ACHIEVED

As Bill C-51 had been introduced in the House of Commons in April 2008, the reform of pharmaceutical regulation was already clearly on the federal government's agenda. Given the delay in re-introducing the legislation, however, it became evident that this was not a high priority for the Conservative government, which held that health care in general was a matter best left to the provinces. But Ottawa is nonetheless responsible for the regulation of pharmaceuticals, and as high-profile lawsuits against large American pharmaceutical companies including GlaxoSmithKline, Eli Lilly, and Pfizer began to emerge, there was increasing concern about improving the regulatory capacity of Health Canada. The driving force for the legislation, however, was the engagement of an influential policy champion, Terence Young, a Conservative back bencher. Young's daughter Vanessa, for whom the law

is named, died at the age of 15 from the effects of a drug, Prepulsid (cisapride), which was still being prescribed even though Health Canada was aware of risks associated with the drug.

5 IMPLEMENTATION AND COMMUNICATION PLANS

Although Vanessa's law was passed into legislation in 2014, certain aspects of the legislation will not come into force until a regulatory framework has been established. Much rests upon the specific articulation of these regulations, including when the Minister should disclose confidential business information, what constitutes a "serious risk," and precisely what kind of clinical trial information will be made public. Two public consultations were conducted after the legislation was passed. The first consultancy period (25 March – 8 June 2015) focused on the development of "operational tools" (including standard operating procedures, guidance documents, process maps, and templates) to assist in the execution of regulations supporting the legislation. A second consultancy (25 March – 25 May 2015) entailed a needs-based assessment asking stakeholders to specify their information needs regarding therapeutic products (what information they require, and when and how it should be made available). On 10 March 2016, Health Canada introduced Draft Guidelines on the disclosure of confidential business information under 21.1(3) of the Act. A 75-day period for stakeholder consultation followed the publication of these Guidelines.

6 EVALUATION

There is widespread consensus that the current legislation is a clear improvement in the regulation of therapeutic products. However, much of the substance of the Act depends upon forthcoming regulations that will provide more specific detail. For example, section 21.71 requires that "prescribed information concerning the clinical trial or investigational test is made public within the prescribed time and in the prescribed manner." This leaves much unsaid. Similarly, it is not clear what criteria will constitute the determination of "a serious risk to injury to human health" (21.1.1 and 21.1.2). Sections 21.31 and 21.32 permit the Minister to require the safety testing of a drug, but it is not clear who would design and conduct the test, and how long they would have to do so. Section 21.8 requires "prescribed health care institutions" to inform the Minister of serious adverse drug reactions; but "health care institutions" are not yet defined (just hospitals? long term care facilities?), and the precise mechanisms of reporting (what and when does one report? how are the reports made? by whom and to whom? what are the consequences for non-reporting?) are also not specified.

A second issue is whether the Minster, through Health Canada, currently has, or will be given, the resources to take advantage effectively of the powers conferred by the Act. Surveys undertaken for Health Canada, for example, noted that only a small number of

individuals were qualified to carry out drug evaluation studies (Soon *et al.* 2010; Wiens *et al.* 2014).

The third issue is whether the discretionary powers granted the Minister will in fact be exercised. Under Vanessa's Law, the Minister "may" require the disclosure of information, the gathering of more data, the relabeling or recall of products, and the imposition of significant fines or injunctions. But the Minister is not obligated to use any of these measures. Prior to the current amendments to the *Food and Drug Act*, Health Canada did have the legal authority to disclose information in order to prevent harm, but it rarely chose to exercise this authority. Some have noted Health Canada's "culture of secrecy" (Herder 2014) as well as Health Canada's "regulatory capture" by the pharmaceutical industry (Lexchin 2013), and remain skeptical that the new powers will markedly change current practices (Herder *et al.* 2014; Lexchin 2016).

A fourth issue is that, while Vanessa's Law requires health care providers to report adverse drug reactions that have been documented, there is no requirement that health care providers document such adverse reactions in the first place. This is because the current process of documentation is unwieldy and inefficient (Hohl, Lexchin, Balka 2015). The comprehensive *reporting* of adverse effects as mandated by the Act may thus require the development of a new framework for the *documentation* of such occurrences.

A final concern is that the law may actually make independent scrutiny of therapeutic products more difficult. The Draft Guidelines presented in March 2016 articulated a very precise framework for the new disclosure powers set out in 21.1(3)(c). Specifically, disclosure is limited to specific kinds of individuals, who must sign a legally binding confidentiality agreement, who cannot reproduce the disclosed information, and who must demonstrate that they have exhausted all other sources of the information requested, "including from the originator of the information." Herder and Lemmens (2016, 14-15) argue that Vanessa's Law does not support the limitations introduced in the Draft Guidelines, and that the Guidelines are *ultra vires* to the extent that they give discretionary powers to the Minister of Health, that are not supported by the Act itself. More bluntly, Herder and Lemmens argue that the obligations imposed by the Guidelines upon those requesting access to data are contrary to the purpose of the Act, "as they aim at protecting and safeguarding alleged commercial interest in the data, which the Minister is explicitly authorized to disregard for the purpose of the protection of public health and safety" (2016, 15). In short, while Vanessa's Law was established with the aim of facilitating the transparency of pharmaceutical regulation, the institutionalization of the Draft Guidelines may potentially make access to information on pharmaceutical data more difficult.

7 STRENGTHS, WEAKNESSES, OPPORTUNITIES AND THREATS

Table 2 presents an analysis of the strengths, weaknesses, opportunities and threats of the introduction of Vanessa's Law and the forthcoming regulations from the perspective of various stakeholders. .

Table 2: SWOT Analysis

Strengths	Weaknesses
• Clear legal basis for compelling authorization holders to provide information, change labels, and recall products • Stronger measures for compliance and enforcement • Stronger legal basis for the collection of adverse effects of drugs and devices • Minister now able to incorporate by reference other documents into the Food and Drug Regulations	• Greater discretionary powers may not be used, thus perpetuating the status quo • No guarantee that Health Canada will be given the resources to be able to implement the measures outlined in the Act • Precise mechanism of post-market surveillance not clearly specified • No effective mechanism for the documentation of adverse drug events
Opportunities	**Threats**
• Greater transparency of data supporting drugs and devices both prior to and subsequent to authorization • Better evidence base for off-label prescribing • More widespread public engagement in the monitoring of therapeutic products • More attractive regulatory basis for emergent biotechnology sector	• Transparency may be stymied by setting out conditions for researchers to access data • Possibility of lawsuits against Health Canada by large multinational drug and device companies for breaching "confidential business information"

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A ORPHAN DRUGS FOR RARE DISEASES

On 3 October 2012, Ottawa announced that it was developing an orphan drug framework for Canada. A draft discussion document on a regulatory framework for orphan drugs was

subsequently presented on 13 December 2012. Why is the development of a regulatory pathway for orphan drugs being pursued independently of Vanessa's Law?

Orphan drugs are pharmaceutical (or biological) products that treat rare diseases. The definition of "rare diseases" varies across jurisdictions, but in Canada they are considered to be diseases that affect less than 1 in 2,000 people. Eight percent of Canadians are affected by a rare disease. The United States implemented a separate regulatory pathway for orphan drugs in 1983, as did the European Union in 2000. The reason these jurisdictions considered orphan drugs separately from other drugs is twofold. The first is due to cost: historically, the tiny market for drugs treating rare diseases made it difficult for pharmaceutical companies to recoup a profit from these drugs. The second is due to the difficulty in establishing a robust evidence base for such drugs: because there are, by definition, so few individuals with a given rare disease within any one jurisdiction, it becomes very difficult to find a large enough cohort for randomized controlled trials.

What does a separate pathway for orphan drugs accomplish? First, it provides economic incentives for pharmaceutical firms to produce new drugs for diseases. These incentives can include scientific and clinical trial protocol advice, priority review, regulatory fee reductions, tax incentives, and post-approval data exclusivity. Second, regulatory structures for orphan drugs move away from a binary yes/no approval process and permit evidence to be collected in "real world" conditions after the drug has been approved. This lifecycle approach, also called "adaptive licensing," permits the regulatory authority to monitor the drug over time and to "fine tune" (or even to rescind) the regulatory approval for the drug given any reported adverse events or changes in its reported effectiveness.

What are the policy issues surrounding the development of a regulatory framework for orphan drugs? Because the vast majority of rare diseases are genetically-based, advances in genomic technology increasingly allow researchers to tailor drugs to particular genetic profiles leading to better diagnostic accuracy, more effective treatment, and better identification of potential adverse events. This approach, also known as "precision medicine," is especially prevalent in oncology. However, the fragmentation of particular cancers into specific genetic "types" means that common diseases (e.g., breast cancer) are being transformed into a number of discrete "rare diseases." In this way, precision medicine has greatly expanded the target market for orphan drugs. Given the widening market for orphan drugs, and given the financial and regulatory incentives now available under the orphan drug regulatory frameworks in other jurisdictions, large pharmaceutical firms increasingly see orphan drugs as a lucrative field. Currently, the median cost-per-patient differential for orphan drugs is 13.8 times higher than non-orphan drugs. The proportion of orphan drugs vis-à-vis non-orphan drugs is set to account for over 20% for all prescription sales globally by 2020 (EvaluatePharma 2015, 6). Thus, Canadians will have to consider whether the American regulatory framework for orphan drugs, which was conceived when "rare diseases" were not comprised of so many genetically-specific variants of common diseases, is in fact the best model at a time when the use and cost of such drugs has increased so dramatically.

Moreover, the American and European regulatory frameworks were designed to accom-

modate research-intensive pharmaceutical industries. The Canadian pharmaceutical sector invests very little in research and development. As the Patented Medicines Prices Review Board (PMPRB) reports, the ratio of research and development to sales has fallen to its lowest level (4.4%) since 1988, when patent protection was renegotiated. In contrast, the seven countries that serve as the reference point for Canada's pharmaceutical sector currently have a collective ratio of 22.8% (PMPRB 2016, 52). The policy question then becomes whether it is worthwhile to provide incentives to an industry that historically has shown little inclination to perform research in Canada, or whether the small-scale (and increasingly lucrative) development of "niche" medicines that is qualitatively distinct from traditional pharmaceuticals can be nurtured through such a regulatory framework.

The second set of policy questions address the regulatory process itself. Regulatory frameworks for orphan drugs are based upon a trade-off: patients get quicker access to orphan drugs, but the evidence base is much more tenuous because the approval process is less rigorous. The weaker evidence base, in theory, is strengthened over time as "real world" data on the effectiveness of these drugs, and their adverse events, is collected from those using these products. In practice, however, there is some doubt whether Canada has the immediate capacity to implement a system of adaptive licensing. Are adverse events systematically being reported? Has Health Canada been willing to follow up vigorously on companies which receive a conditional notice of compliance? Does Canada have an effective institutional infrastructure (such as rare disease registries) for collecting and coordinating data? Do public or private insurance agencies have access to this data so that patients with rare diseases can be remunerated for effective treatments? Until these questions can be answered in the affirmative, a rigorous regulatory framework for orphan drugs may not be feasible.

Currently, Canadians have access to orphan drugs through Health Canada's Special Access Programme, or through participation in clinical trials. There is general agreement that these processes are not optimal. A first round of consultation on a regulatory system for orphan drugs was conducted by the House of Commons Standing Committee on Health in May 2016. Health Canada expects the process of consultation to be finished by the end of 2017. The regulatory framework provided by Vanessa's Law does facilitate the establishment of a regulatory system specifically for orphan drugs by providing greater oversight authority to the Minister of Health. However, the unique challenges posed by rare diseases, along with the burgeoning field of precision medicine, the nature of the pharmaceutical sector in Canada, and the need for considerable institutional infrastructure, make the regulatory landscape for orphan drugs a very complex policy discussion.

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