

## Regulating prescription drugs for patient safety: Does Bill C-17 go far enough?

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Canada was the last developed country in the world to remove thalidomide from the market, and doing so required an Act of Parliament. At the request of Health Canada's then Food and Drug Directorate, thalidomide's two manufacturers voluntarily withdrew the drug from the market on Mar. 2, 1962.<sup>1</sup> However, most of the drug's distribution was in the form of free samples to medical professionals, which the directorate had no legal authority to control.<sup>2</sup> Therefore, to avoid similar situations in the future and to stop sales of thalidomide, on Dec. 4, 1962, the Parliament of Canada amended the Food and Drugs Act, allowing the distribution of drug samples only under "prescribed conditions" and prohibiting the sale of any drug listed in Schedule H of the act, including thalidomide.<sup>3</sup> The legislation stopped short of granting legal authority to the directorate to unilaterally recall drugs, even though officials recognized that "the co-operation of the manufacturer to recall a drug from the market could not be solely relied on."<sup>2</sup>

More than 50 years later, this gap in Canada's Food and Drugs Act<sup>4</sup> remains: the regulator, Health Canada, cannot order a drug recall. Instead, it must *negotiate* drug recalls with manufacturers. Negotiation invites delay<sup>5</sup> and may precipitate harm to patients that could have been avoided. Several recent examples, including the acne drug cypoterone acetate–ethinyl estradiol (Diane-35),<sup>6</sup> the diabetes drug rosiglitazone (Avandia), the pain-relief drug propoxyphene (Darvon-N), the gastroesophageal reflux drug cispripide (Prepulsid), and the anti-inflammatory drug rofecoxib (Vioxx), illustrate the adverse consequences that may flow from manufacturers' indecision about whether and when to issue a recall, and the regulator's inability to compel one. (Table 1 lists drugs withdrawn for safety reasons from the Canadian market after Aug. 1, 2004.) Drug withdrawals are relatively rare in Canada. However, the fact that some of those withdrawn had been very widely prescribed means that tens of thousands of Canadians were exposed to potential harm after safety issues first arose but before market withdrawal.<sup>7</sup>

Bill C-17, An Act to Amend the Food and Drugs Act, was introduced into Parliament on Dec. 6, 2013, and promises to finally fix this fundamental flaw in Canada's legislation. Proposing revisions to the Food and Drugs Act, including the addition of a power to recall drugs, the bill has been dubbed the Protecting Canadians from Unsafe Drugs Act (Vanessa's Law). (Table 2 summarizes Bill C-17's key provisions.) If enacted, Bill C-17 would represent a substantial improvement over the status quo. Yet, Bill C-17 by no means offers a comprehensive solution to the many problems that have plagued the development, regulation and safe use of prescription drugs in the 50-plus years since thalidomide was withdrawn from the market. Drug manufacturers have engaged in selective reporting to regulators about the evidence base behind new drugs, thereby enhancing the likelihood of receiving market approval.<sup>8</sup> Moreover, a close-knit, conflicted relationship has been observed to exist between manufacturers and regulators at times.<sup>9–11</sup> Therefore, in addition to outlining four elements of the proposed legislation that are welcome improvements to the status quo, we detail six critical elements to add to Bill C-17 to further fulfill the bill's core goal of protecting patient safety.

### Important and welcome elements in the proposed legislation

#### Power to recall drugs

Bill C-17 empowers the Health Minister to issue a recall, without first entertaining representations from the manufacturer, provided he or she

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#### KEY POINTS

- Bill C-17, An Act to Amend the Food and Drugs Act, was introduced into Parliament by the federal government on Dec. 6, 2013.
- If enacted, Bill C-17 would give Health Canada the legal power to recall drugs.
- To meet Bill C-17's core goal of ensuring patient safety, key provisions to improve the transparency of clinical trials and regulatory decision-making must be added to the proposed legislation.

“believes that a therapeutic product presents a serious or imminent risk of injury to health.” Currently, the Health Minister may suspend a manufacturer’s licence to sell a drug,<sup>12</sup> but he or she cannot require the drug to be removed (i.e., recalled) from pharmacy shelves. Only the manufacturer can do so. This parallels the present situation in the United States.<sup>13</sup> The voluntary nature of drug recalls in both jurisdictions has, on occasion, precipitated harmful delays and may undermine regulators’ ability to communicate safety information to the public in a timely fashion. Thus, we contend that Bill C-17’s recall provision constitutes an essential addition to the Health Minister’s powers and should be lauded.

### Power to overcome information asymmetries

Bill C-17 enables the Health Minister to compel manufacturers to provide information about drugs. This is a crucial function because manufacturers are likely to have the greatest real-time knowledge about the safety and effectiveness of the drugs they market.<sup>14</sup> One proposed

amendment states, “If the Minister believes that a therapeutic product may present a serious risk of injury to human health, the Minister may order a person to provide the Minister with information ... to determine whether the product presents such a risk.” Similarly, another proposed provision requires health care institutions to provide information “about a serious adverse drug reaction that involves a therapeutic product or a medical device incident that involves a therapeutic product.” These information-sharing requirements are a major improvement on the status quo.

### Power to enforce conditions on market authorizations and compel changes to product labels

Bill C-17 gives the Health Minister powers to enforce conditions associated with any market authorization granted to manufacturers (also known as a “Notice of Compliance with Conditions”<sup>15</sup> as opposed to the standard “Notice of Compliance”). Holders of market authorizations will be required to comply with any “terms and

**Table 1.** Drugs withdrawn for safety reasons from the Canadian market after Aug. 1, 2004

Drug, generic (brand) name	Approval date or date listed in the <i>Compendium of Pharmaceuticals and Specialties</i> *	Withdrawal date†	Reason for withdrawal
Rofecoxib (Vioxx)	Oct. 25, 1999	Sept. 30, 2004	Increased relative risk of cardiovascular events
Valdecoxib (Bextra)	Dec. 11, 2002	Apr. 7, 2005	Life-threatening skin reactions
Thioridazine (Mellaril)	1959	Sept. 30, 2005	Cardiac dysrhythmias
Estradiol dienanthate–estradiol benzoate and testosterone enanthate (Climacteron)	1961	Oct. 22, 2005	Endometrial hyperplasia/carcinoma
Gatifloxacin (Tequin)	Jan. 9, 2001	June 29, 2006	Serious disorders of glucose metabolism
Tegaserod (Zelnorm)	Mar. 12, 2002	Mar. 30, 2007	Increase in cardiovascular ischemic events
Pergolide (Permax)	June 27, 1991	Aug. 30, 2007	Valvulopathy
Lumiracoxib (Prexige)	Nov. 2, 2006	Oct. 3, 2007	Risk of serious hepatotoxicity
Efalizumab (Raptiva)	Oct. 24, 2005	Feb. 22, 2009	Progressive multifocal leukoencephalopathy
Sibutramine (Meridia)	Dec. 28, 2000	Oct. 8, 2010	Serious cardiovascular events
Dextropropoxyphene (Darvon-N)	1961	Nov. 25, 2010	Risk of serious abnormal heart rhythms
Sitaxsentan (Thelin)	June 19, 2007	Dec. 15, 2010	Idiosyncratic hepatotoxicity
Calcitonin (synthetic, salmon) nasal spray (Miacalcin)	July 13, 1992	Oct. 1, 2013	Increased rate of malignancies
Meprobamate-containing medicine (282-MEP)	Nov. 1, 1998	Oct. 28, 2013	Risk of overdose, abuse or misuse

\*Approval dates are from Health Canada’s Notice of Compliance website: [www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/index-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/index-eng.php). For drugs approved before Jan. 1, 1991, the date of approval is the date that the product was first listed in the *Compendium of Pharmaceuticals and Specialties*.

†Withdrawal dates are from Health Canada’s MedEffect website: [www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/index-eng.php](http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/index-eng.php). Withdrawal of gatifloxacin was not mentioned on the MedEffect website but was confirmed on Health Canada’s Drug Product Database: [www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php).

conditions of the authorization that are imposed under regulations.” This new power is essential given that, since 1998, about one in 14 new prescription pharmaceuticals and biologics have been approved by Health Canada on the condition that they undertake further postmarket stud-

ies pursuant to a Notice of Compliance with Conditions (estimate based on annual reports [1998–2012] from the Therapeutic Products Directorate and the Biologics and Genetic Therapies Directorate, available on request from publications@hc-sc.gc.ca). With regulatory modernization

**Table 2.** A summary of key provisions in Bill C-17, An Act to Amend the Food and Drugs Act

Focus	Proposed section(s)
Power to recall drugs	21.3(1) — If the Minister believes that a therapeutic product presents a serious or imminent risk of injury to health, he or she may order a person who sells the product to (a) recall the product; or (b) send the product, or cause it to be sent, to a place specified in the order.
Power to overcome information asymmetries	21.1 — If the Minister believes that a therapeutic product may present a serious risk of injury to human health, the Minister may order a person to provide the Minister with information that is in the person’s control and that the Minister believes is necessary to determine whether the product presents such a risk.  21.6 — No person shall knowingly make a false or misleading statement to the Minister — or knowingly provide him or her with false or misleading information — in connection with any matter under this Act concerning a therapeutic product.  21.8 — A prescribed health care institution shall provide the Minister, within the prescribed time and prescribed manner, with prescribed information that is in its control about a serious adverse drug reaction that involves a therapeutic product or a medical device incident that involves a therapeutic product.
Power to enforce conditions on market authorizations, modify product labels and require assessments, tests, studies, etc.	21.7 — The holder of a therapeutic product authorization shall comply with the terms and conditions of the authorization that are imposed under regulations.  21.2 — The Minister may, if he or she believes that doing so is necessary to prevent injury to health, order the holder of a therapeutic product authorization that authorizes the import or sale of a therapeutic product to modify the product’s label or to modify or replace its package.  21.31 — Subject to the regulations, the Minister may order the holder of a therapeutic product authorization to conduct an assessment of the therapeutic product to which the authorization relates and provide the Minister with the results of the assessment.  21.32 — Subject to the regulations, the Minister may, for the purpose of obtaining additional information about a therapeutic product’s effects on health or safety, order the holder of a therapeutic product authorization to (a) compile information, conduct tests or studies or monitor experience in respect of the therapeutic products; and (b) provide the Minister with the information or the results of the tests, studies or monitoring.  30(1.2)(b) — Without limiting the power conferred by any other subsection of this section, the Governor in Council may make regulations ... authorizing the Minister to impose terms and conditions on authorizations ... including existing authorizations, and to amend those terms and conditions.
Serious enforcement measures	31.2 — Subject to section 31.4, every person who contravenes any provision of this Act or the regulations, as it relates to a therapeutic product, or an order made under any of sections 21.1 to 21.3 is guilty of an offence and liable (a) on conviction by indictment, to a fine not exceeding \$5 000 000 or to imprisonment for a term not exceeding two years or to both; and (b) on summary conviction, for a first offence, to a fine not exceeding \$250 000 or to imprisonment for a term not exceeding six months or to both and, for a subsequent offence, to a fine not exceeding \$500 000 or to imprisonment for a term not exceeding 18 months or to both.  31.4 — A person who contravenes section 21.6, or who knowingly or recklessly causes a serious risk of injury to human health in contravening another provision of this Act or the regulations, as it relates to a therapeutic product, or an order made under any of sections 21.1 to 21.3 is guilty of an offence and liable (a) on conviction on indictment, to a fine the amount of which is at the discretion of the court or to imprisonment for a term not exceeding five years or to both; and (b) on summary conviction, for a first offence, to a fine not exceeding \$500 000 or to imprisonment for a term not exceeding 18 months or to both and, for a subsequent offence, to a fine not exceeding \$1 000 000 or to imprisonment for a term not exceeding two years or to both.  31.7 — If an offence under section 31.2 or 31.4 is committed or continued on more than one day, it constitutes a separate offence for each day on which it is committed or continued.

pushing for faster access to drugs, Health Canada is poorly positioned to enforce such postmarket conditions without this new power.<sup>16</sup> Furthermore, at present it can take several months to negotiate labelling changes despite clear safety concerns.<sup>16</sup> In 2007, the US Food and Drug Administration (FDA) was granted powers to enforce conditions and to compel changes to a product's label in light of safety concerns that emerge after market approval.<sup>17</sup> It is imperative that Health Canada be vested with these powers.

### **Serious enforcement measures**

Finally, Bill C-17 creates much stronger penalties for failure to comply with some of the provisions of the Food and Drugs Act and accompanying regulations. These include fines of up to \$5 million per day during which the offence is committed, and/or imprisonment for the most egregious offences (e.g., failure by a seller to comply with a recall of a therapeutic product ordered by the Health Minister).

Each of these proposed amendments to the current Food and Drugs Act should be embraced. However, additional elements are badly needed to address patient safety at the federal level.

### **Elements that should be added to the proposed legislation**

#### **Enhance the power of recall and alter the ability to suspend**

The proposed recall power could be improved in at least three ways. First, the existing power to “suspend” market authorizations (as opposed to issuing a drug recall) for reasons of safety is apparently limited to instances where the Health Minister “considers that the drug is not safe ... as shown by evidence.”<sup>12</sup> This sets a high bar; in our view, the Health Minister should be empowered to suspend market authorizations where he or she has reasonable grounds to believe a suspension will avoid potential injury to human health. Furthermore, the ability to recall (and suspend) should not be limited to those who sell the product. Elsewhere in Bill C-17, the focus is on holders of “therapeutic product authorizations,” so one can infer that sellers and holders of therapeutic product authorizations are not the same entities — the company holding the authorization may, for instance, license distribution to another company. The Health Minister should be explicitly empowered to issue suspensions and recalls to both types of “persons.”

Finally, terms such as “injury” and “harm” are open to restrictive interpretation. Health Canada recently took the position that a pregnancy

caused by faulty birth control medication is not a “serious adverse health consequence” but rather a “lifestyle choice.”<sup>18</sup> Therefore the medication is in a lower risk classification for recall unless the woman should not get pregnant specifically for medical reasons.<sup>19</sup> The terminology in Bill C-17 needs to be clarified and definitions provided to prevent such restrictive interpretation.

#### **Exempt the Health Minister from liability for drug suspensions and recalls**

In the event that a market authorization is suspended or a drug recalled, a manufacturer or seller may attempt to sue the government for damage to product sales. This possibility is a strong disincentive to invoking the power to suspend or recall, and may colour the Health Minister's interpretation of when a “potential harm” (for suspensions) or “serious or imminent risk” to health (for recalls) is present. Given the potential difficulties in rapidly establishing a definitive causal link between a given drug and observed adverse events, an exemption from liability for lost product sales or other injury to the manufacturer or seller should be added. This would ensure that the Health Minister can invoke these powers in good faith on a precautionary basis when he or she has reasonable grounds to believe that a drug poses a safety issue and would restrict the ability of a manufacturer or seller to succeed in a lawsuit.

#### **Ensure transparency in clinical trials**

Clinical trial data should be regarded as a public good,<sup>20</sup> and the need for greater transparency in the evidence base behind therapeutic drugs is well documented.<sup>21,22</sup> Several jurisdictions including the US<sup>23</sup> and Europe<sup>24</sup> have established a legal requirement to register clinical trials. The European Medicines Agency has announced a proactive policy to release full clinical trial reports submitted by manufacturers for market authorization,<sup>25</sup> and is exploring the possibility of releasing anonymized patient-specific clinical trial data. Canada has done neither to date. The clinical trials database created last year identifies ongoing clinical trials but does nothing to ensure that the evidence generated by those trials is open to independent and timely scrutiny.<sup>26</sup> Registration of clinical trials is not a panacea.<sup>27,28</sup> However, requiring registration by law, and creating a robust mechanism to enforce that requirement, is an important step toward improving the transparency of the evidence base behind drugs and other therapies, and avoiding potential harm to patients.<sup>29</sup> In addition, making sure that clinical trial data, whether collected before market approval or in postmarket studies, are available for scrutiny by independent researchers is critical

to ensuring that treatment and use decisions are evidence-based.<sup>30</sup>

### **Enhance transparency in Health Canada's decision-making**

A related issue is the transparency of Health Canada's own decision-making. At present, Health Canada publishes limited information solely on a subset of its decisions, specifically, on drugs approved for sale and high-risk medical devices.<sup>31</sup> The European Medicines Agency, in contrast, also publishes its "negative opinions" to ensure that health care providers and patients are aware of drugs not approved for certain indications because of safety or efficacy issues identified during clinical trials.<sup>32</sup> This aids in averting underinformed off-label prescribing by physicians. The FDA in the US has tabled a proposal to do the same in the name of patient safety.<sup>33</sup> Bill C-17 should empower Health Canada to publish both positive and negative regulatory decisions. At minimum, Health Canada should publish the rationales for decisions concerning all drugs approved for sale, drugs refused for reasons of safety or efficacy, and drugs that are suspended or recalled.<sup>34</sup> Presently, the regulator's rationale is not transparent even when drugs are withdrawn from the market for safety reasons,<sup>5,35</sup> or, conversely, when they remain on the market following a safety review, as with cypoterone acetate–ethinyl estradiol (Diane-35)<sup>6</sup> or rosiglitazone (Avandia). Bill C-51, which also proposed amendments to the Food and Drugs Act but died on the Order Paper in 2008, included a provision allowing the Health Minister to "disclose to the public information about the risks or benefits that are associated with a therapeutic product."<sup>36</sup> The omission of such a provision in Bill C-17 must be rectified.

### **Outline clear limits to the scope of proprietary information**

Meaningful transparency is hard to achieve in practice, in part because manufacturers often claim that the government is obliged to protect information about the safety and efficacy of a drug as "proprietary," either as a "trade secret" or as "confidential business information."<sup>37</sup> These assertions overstate what the law actually requires and prevent important information about safety and effectiveness from being released.<sup>37</sup> International treaties simply require Canada to protect trade secrets and confidential business information without specifying the scope of those types of information. No Canadian court decision indicates that information about the safety or efficacy of a drug is proprietary, and current case law casts doubt on any such assertion. In principle, Health

Canada can at present disclose greater amounts of safety and efficacy information. However, to clarify and to overcome manufacturers' efforts to resist disclosure, Bill C-17 should explicitly state that the results of clinical trials, including de-identified patient-level data, postmarket studies, and adverse drug reactions reported by drug manufacturers and health care institutions, are not proprietary and therefore should be publicly disclosed.

The European Medicines Agency was concerned that failure to disclose clinical trial results undermines trust in the regulatory system and ignores the contribution to knowledge generation by clinical trial participants. Therefore, it has taken the stance that trial results are nonproprietary and is moving steadily toward requiring proactive publication of all clinical trial data for drugs it reviews.<sup>38</sup> Even manufacturers are beginning to acknowledge that, far from undermining innovation, greater disclosure of clinical trial data represents a potential boon to their research and development efforts.<sup>39,40</sup> It is incumbent on Canada to move in the same direction.

### **Do not allow trade to trump patient safety**

Bill C-17 gives the Governor in Council scope to impose stringent rules favouring data protection to the detriment of other powers in the Food and Drugs Act. This proposal is fundamentally problematic and must not be enacted. It is true that Canada must, under treaties such as the North American Free Trade Agreement, protect data (including clinical trial data) against "unfair commercial use."<sup>41</sup> However, under current law there is broad discretion about how to do so,<sup>42</sup> and any steps taken in the name of data protection are not meant to limit other measures in the Food and Drugs Act that protect patient safety. The Food and Drugs Act should remain as presently worded to preserve the broad discretion of the Health Minister; it should not be amended as proposed in Bill C-17.

## **Conclusion**

Bill C-17 is an important step toward the safe regulation of drugs because it enhances the ability of Health Canada to act in the face of threats to public health. It also introduces meaningful enforcement mechanisms, including substantial penalties, for noncompliance. However, it requires amendment to incorporate several additional key components of prescription drug safety. Bill C-17 has the potential to make an important and positive difference to public safety in Canada. We urge that Bill C-17 be revised and enhanced before it becomes law so that this potential can be realized.



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