

BMJ Open

Substandard and falsified medicines in Canada: a retrospective review of risk-communication documents (2005–2013)

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-006088
Article Type:	Research
Date Submitted by the Author:	10-Jul-2014
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Primary Subject Heading:	Public health
Secondary Subject Heading:	Health policy, Pharmacology and therapeutics
Keywords:	Substandard medicines, Falsified medicines, Drug recalls

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Manuscripts

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3 **Substandard and falsified medicines in Canada: a**
4 **retrospective review of risk-communication documents**
5 **(2005–2013)**
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40 **Abstract:** 226 words

41 **Full text:** 2500 words

42 **Number of figures:** 3

43 **Number of tables:** 3
44
45
46
47
48
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51 **Keywords:** Falsified, substandard, defective, medicines, recalls
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ABSTRACT

Objective: To explore the problem of substandard and falsified medicines in Canada.

Design: A retrospective review of drug recalls and risk-communication documents.

Setting: The Health Canada website search for drug recalls and risk-communication documents issued between 2005 and 2013.

Eligibility criteria: Drug recalls and risk-communication documents related to quality defect in medicinal products.

Main outcome measure: Relevant data about defective medicines reported in drug recalls and risk communication documents, including description of the defect, type of formulation, year of the recall and category of the recall or the document.

Results: There were 653 defective medicines of which 649 were substandard. The number of defective medicines reported by Health Canada increased from 42 in 2005 to 143 in 2013. The two most frequently reported types of defects were stability (205 incidents) and contamination issues (139 incidents). Some of these defects were found to be more prominent and repetitive over other types within some manufacturers. Tablet formulation (251 incidents) was the formulation most frequently compromised. There were four falsified medicines reported over the nine-year period.

Conclusions: Substandard medicines are a significant problem in Canada. Their incidence appears to be increasing and they have resulted in a significant number of recalled medicines. Most of the failures were related to stability issues, raising the need to investigate the root causes and for stringent preventative measures to be implemented by manufacturers.

Strengths and limitations of this study

- It is the first review to assess the problem of substandard and falsified medicines in Canada.
- It quantifies and analyses drug recalls in Canada over a 9- year period.
- Clinical significance of the problem is undetermined, owing to the lack of data from Health Canada regarding adverse events associate with the use of defective medicines.

INTRODUCTION

Substandard and falsified medicines are a major public health dilemma.¹⁻⁴ Different surveys in lower income countries (LIC) and lower-middle-income countries (LMIC) have found that substandard and falsified medicines are readily available.^{4, 5} There has been, however, relatively little evidence about the impact of this problem in high income countries (HIC) such as Europe and North America.⁴ HIC rely on their national drug regulatory authorities to safe guard the public from the danger of poor quality medicines, as the regulation of medicines are well developed compared to LIC and LMIC.⁶ In our previous study on the UK we have shown that substandard medicines are significant problem and appear to be increasing.⁷ We wished to explore another HIC and chose Canada, as we have previously studied a European country.

In Canada, Health products are regulated by Health Canada, which is the federal department responsible for the monitoring and regulating of medicines.⁸ It issues a number of risk-communication documents to the public and healthcare professionals. These involve identification of the possible risk, assessment of its severity and clarification of the nature of the problem. This communication is established also to initiate and disseminate information regarding defective medicines or existing health risks to allow patients and healthcare professionals to make the right decision.⁹

The aims of this study were to quantify and describe the pattern of drug recalls and risk-communication documents issued by Health Canada and to explore the problem of substandard and falsified medicines in this setting.

METHODS

Health Canada defines falsified health product (traditionally known as counterfeit) as “one that is represented as, and likely to be mistaken for, an authentic product. Counterfeiting can apply to both branded and generic products, and could relate to a product's identity or source, could include products with the correct ingredients/components, with the wrong ingredient/components, without active ingredients, with insufficient active ingredients or with misleading packaging or labelling.”¹⁰ This definition is similar to the 1992 WHO definition of counterfeit medicine, which has since been updated by the WHO.¹¹ A substandard medicine is a medicine which does not meet its established quality standards.¹²

A search for defective medicines (i.e., substandard and falsified medicines) was carried out. This was performed through the official Health Canada's website and using the search engine allocated for advisories, warnings, and recalls of health products. Health Canada started posting health product recalls on its website in 2005, thus all recalls issued between 2005 and 2013 were included. All risk-communication documents (advisories, warnings, letters to health professionals and recalls) were reviewed and the relevant information was then extracted.⁹ All relevant information regarding defective health products was compiled and exclusion criteria were as follows: medicines lacking efficacy, herbal and probiotic products; dietary and cosmetic products; veterinary medicines; medicines recalled for regulatory reasons; and other health products, such as alcohol swabs and gases. The following data were extracted from the health product recall: name, strength, and dosage form; year of the recall; number of affected batches; nature of the defect; class of drug recall; and action taken regarding defective medicine. Three types of drugs can be distinguished from risk-communication documents; substandard drugs, falsified drugs and drugs withdrawn due to severe adverse drug reactions. The decision on which incident was falsified or substandard is that published by Health Canada.

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3 The type of defect were then classified using the same defect classification
4 used in our previous study.⁷ The quality defects were classified as
5 contamination, minor or major packaging defect, delivery (e.g., leaking bags)
6 defect, stability failure, potency issues, active ingredient defect and other
7 issues (such as other deviations concerning non-compliance with good
8 manufacturing practice at manufacturing site).
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14 The WHO Organization Anatomical Therapeutic Chemical (ATC)
15 Classification System was used to classify the total number of defective
16 medicine incidents obtained.¹³ The first two levels of this classification were
17 used.
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20 21 **RESULTS**

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24 A total of 653 defective medicines were identified in the Canadian supply
25 chain (Figure 1). Among these defective medicines, 649 were found to be
26 substandard medicines, and only four were found to be falsified medicines in
27 the nine years studied. The rate of reporting defective medicines has
28 increased each year over the last six years (Figure 2).
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32 33 **Substandard medicines**

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35 Substandard medicines represent the bulk of defective medicines (649
36 medicines, 99%) reported by Health Canada. The two most frequent types of
37 defects reported were stability (205 incidents) and contamination (139
38 incidents) issues (Table 1). Stability of formulations was a significant problem.
39 The majority of these formulations were found to have degraded one year
40 after their release into the market, resulting in low concentrations of active
41 ingredients, impurities, dissolution and disintegration failures. Tablets were
42 the formulation most frequently reported to be substandard (supplementary
43 table 1).
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51 Among the 649 substandard medicines, 89 were subjected to urgent recalls.
52 More than half of these medicines (46, 53%) were parenteral formulations
53 (Tables 2 and 3). Of the 89 medicines that were recalled, 34 were
54 contaminated. The majority of these were parenteral formulations that were
55 recalled due to the presence of particulate matters, the presence of microbes,
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3 or a lack of sterility assurance during their manufacture (Table 2). The
4 remaining substandard medicines (55) were urgently recalled due to other
5 types of defects (Table 3), mainly packaging defects or delivery issues (such
6 as cracks in the vials or leaks in the bags, as well as faults in the unit used to
7 deliver the medicines). Packaging defects were one of the major clinical
8 issues reported, and these included incorrect labelling (i.e., wrong drug name,
9 strength, or expiry date) and packaging that lacked important information
10 regarding safety or the use of medicines in the patient information leaflets. In
11 some cases, the labelling was correct, but the wrong medicines were filled,
12 resulting in major and urgent recalls of affected batches (Table 3).
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21 Drugs that act on the nervous system (141/649), alimentary tract and
22 metabolism (90/649), and cardiovascular system (83/649) were the subgroups
23 that most frequently contained substandard medicines. When the second
24 level of this classification (i.e., therapeutic classification) was used, the top
25 three groups reported to be substandard were analgesics (65/649),
26 antihypertensives (50/649) and antibacterials (38/649) (supplementary table
27 2).
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33 **Substandard medicines categorised by manufacturers**

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35 The review identified 148 manufacturers that were holding the marketing
36 authorisation for 649 recalled medicines. All manufacturers that held the
37 marketing authorisation of 8 or more recalled medicines are listed in
38 supplementary table 3. It was noted that 50% or more of substandard
39 medicines manufactured by Apotex Inc., Pfizer Canada Inc. and Laboratoire
40 Riva Inc. had stability issues. Almost half of the substandard products from
41 Baxter Co., Hospira Healthcare Co. and GlaxoSmithKline Inc. were
42 contaminated. Products of Sandoz Canada Inc. had a problem with the active
43 ingredient, which was either too high or too low. More than half of Novartis
44 products, which are reported to be substandard, were recalled due to delivery
45 concerns, such as failure of the child-resistant feature of the bottle cap or
46 leaks in the infusion bags.
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Falsified medicines

Four incidents of falsified medicines were identified in Canada's supply chain in 2010, 2011 and 2013. The first incident occurred in 2010 with a falsified Viagra® (sildenafil) product, a sexual enhancement medicine. Details on specific quality defects for this medicine were not provided. The second incident occurred in 2011 with a counterfeit Cialis® (tadalafil), which is also a sexual enhancement medicine. Analysis of the counterfeit revealed that this product contained sildenafil, which is the active ingredient in Viagra®, whereas genuine Cialis contains the active ingredient tadalafil. Two other incidents of falsified Cialis® and Viagra® were also reported in 2013, which were found in retail shops. The falsification was confirmed in cooperation with the legitimate manufacturers of Cialis (i.e., Eli Lilly) and Viagra (i.e., Pfizer).

DISCUSSION

This is the first review that discusses the issue of substandard and falsified medicines in Canada by evaluating the risk-communication documents and drug recalls posted on Health Canada website. Our observations of defective medicines recalls over nine consecutive years, from 2005 to 2013, have shown that the recall of substandard medicines is an increasing trend. It is concerning that over half of the stability failures were related to instability of active ingredients or dissolution and disintegration failure. Both defects have the potential to affect the bioavailability of the active ingredients in the systemic circulation, and in turn, may lead to therapeutic failure.

Substandard medicines

The most frequent type of formulation reported to be substandard were tablets. Tablets have a slow onset of action and require less precaution in terms of sterility, than parenteral formulations. The extent of adverse consequences that can arise from failure to comply with manufacturing requirements, however, cannot be ignored. This was evident from the death of 120 patients in Pakistan due to contamination of isosorbide mononitrate tablets with large doses of an antimalarial drug.¹⁴ Another of the most pronounced examples is the phenobarbital and morphine tablet recalls in

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3 Canada. Oversized tablets (i.e. tablets that exceed the weight requirement)
4 were found in both drugs, raising the risk of the patients to have as much as
5 double the strength stated on the bottle (Table 3). The Institute for Safe
6 Medication Practices (ISMP), a non-profit organisation, stated that the US
7 manufacturer (KV Pharmaceutical) received abnormally high reports of
8 serious adverse events concerning overdose.¹⁵ Adverse events relating to this
9 defect have not been documented by Health Canada.
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16 It was uncertain whether the rise of substandard medicines incidents were
17 related to improved detection by Health Canada or due to an increase of
18 substandard medicine production by manufacturers. The rate of increased
19 incidence of substandard medicines can be correlated with the
20 implementation of improved detection policies and regulations by Health
21 Canada. Introduction of GMP inspection policy for Canadian drug
22 establishments may be one of the explanations.¹⁶ In January 2008, Health
23 Canada introduced this policy as a response to increasing demand to update
24 its policy on GMP, given that so many GMP guidelines and international
25 agreements had been made since 1996. Subsequently, there has been a
26 steady increase of incidents of substandard medicines from 2008 to 2013
27 (Figure 2). This policy illustrates the procedures that the Health Products and
28 Food Branch (HPFB) follows to ensure that manufacturing sites, distributors
29 and wholesalers are complying with GMP. It is conducted via inspections by
30 the HPFB inspectorate with varying cycles, which depend on an approach that
31 takes risk assessment into consideration, and a ranking scale of priority.¹⁶
32 Similarly, it has been highlighted that most of the FDA recalls were related to
33 FDA inspectors' visits in the USA.¹⁷
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47 Canada and the UK are two of the top pharmaceutical markets in the world,
48 holding equal global pharmaceutical market share values of USD \$21,877 and
49 USD \$21,635 billion, respectively.¹⁸ A larger number of substandard
50 medicines were found in the Canadian supply chain (649 medicines) than in
51 the UK (280 medicines).⁷ The major contributor to this difference in our data
52 was the number of medicines recalled due to stability problems (Figure 3),
53 which were responsible for 50% of the difference. The differences in stability
54 issues between Canada and the UK require further investigation.
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Falsified medicines

There were only four incidents of falsified medicines reported by Health Canada in the nine-year period, reported in 2010, 2011 and 2013. In contrast, 11 falsified cases were reported in the UK by the MHRA between 2004 and 2009.⁷ In 2010, Health Canada, under the HPFB, published a policy regarding falsified medicines.¹⁰ The aims of the policy are to outline the procedures that are to be carried out in order to tackle the problem. This includes disseminating educational programmes, assessing and identifying the risks, and building bridges between various government organisations in order to undermine the risk. Such organisations include the Canada Border Service Agency (CBSA) and Royal Canadian Mounted Police (RCMP).¹⁰

In 2009, more than 15,000 falsified tablets were seized by the RCMP in raids against illegal drugs trade in the Montreal region, such as Viagra and cancer drugs. Analysis of these samples was conducted by Health Canada.^{19, 20} The presence of falsified medicines in the official supply chain was also reported by the Criminal Intelligence Service Canada. Pharmacy staff of two pharmacies in Ontario were charged for deliberate sale of falsified medicines. These drugs contained the wrong or no active pharmaceutical ingredient. Eleven patients of one pharmacy died after taking Norvasc (amlodipine besylate) tablets, a prescription drug for hypertension and angina. Investigation of the deaths was carried out by the Ontario Coroner's Officer. It revealed that the manner of death was "undetermined" and the cause of death was due to "possible unauthorized medication substitution" in four out of 11 deaths.²¹ According to the RCMP, the problem of falsified medicines is a growing trend in Canada.^{20, 22} However, Health Canada reports on falsified medicines do not reflect this trend; which means that this problem may be underreported.

Manufacturing errors and investigation of the root cause

It is the responsibility of the manufacturers and marketing authorisation holders to recall their defective products after consultation with Health Canada. The majority of these recalls were issued by the manufacturers or marketing authorisation holders using the health product notice type 1, 2 or 3, which

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3 accounted for 95% of the total recalls. Stability issues were mainly identified by
4 the manufacturers during on-going stability testing. However, it is unknown
5 whether these defects were identified by internal auditing systems of the
6 manufacturers, by intervention of the Health Canada inspection team or by
7 reports from healthcare professionals.
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12 Analysing pharmaceutical product recalls can be of great importance to identify
13 the root causes of recalled medicines. The prompting of a drug recall can be
14 regarded as a disastrous failure of the manufacturer's quality plan. Even with
15 stringent quality measures, errors can occur.^{23,24} Thus, it is very important to
16 identify the root cause of the defects to avoid similar episodes in the future. It
17 has been highlighted in this review that stability failure and contamination issues
18 were the defect types being reported most frequently. These issues affected
19 several manufacturers on more than one occasion (supplementary table 3). This
20 highlights the need for root cause investigations and appropriate measures to be
21 implemented by manufacturers.
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29 **Limitations**

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32 This study encountered some limitations. Firstly, the expected adverse events
33 associated with the use of substandard and falsified medicines were not
34 reported by Health Canada or the manufacturers. Moreover, we were not able
35 to compare the expected risk with the pharmacovigilance data in Canada, as
36 this data is not in the public domain. Thus, the clinical significance of the
37 problem is unknown. Secondly, there are currently scarce reports about
38 falsified medicines on Health Canada website and on other official
39 government websites, such as the RCMP and CBSA. The extent of this
40 problem, therefore, cannot be determined.
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48 **CONCLUSION**

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50 Substandard medicines are a significant problem in Canada. Their incidence
51 appears to be increasing and they have resulted in a significant number of
52 recalled medicines. Most of the failures were related to stability issues, raising
53 the need to investigate the root causes and for stringent preventative
54 measures to be implemented by manufacturers. Regular GMP inspections on
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3 manufacturing sites were highlighted in this review as some of the most
4 important tools that can improve detection of substandard medicines.
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7 **Contributors:**

8 TA and IC conceived the study design and planned the research. TA
9 performed the database search, extracted the data and drafted the
10 manuscript. HS double-checked the extracted data, and interpreted the
11 results. IC and HS edited and reviewed the manuscript. All authors approved
12 the final version of the manuscript.
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19 **Competing interests:** None.
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22 **Funding:** This research received no specific grant from any funding agency in
23 the public, commercial or not-for-profit sectors.
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27 **Ethical approval:** Not required.
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30 **Data sharing:** No additional data available.
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TABLES AND FIGURES

Figure 1: Flow diagram of search and resulting incidents

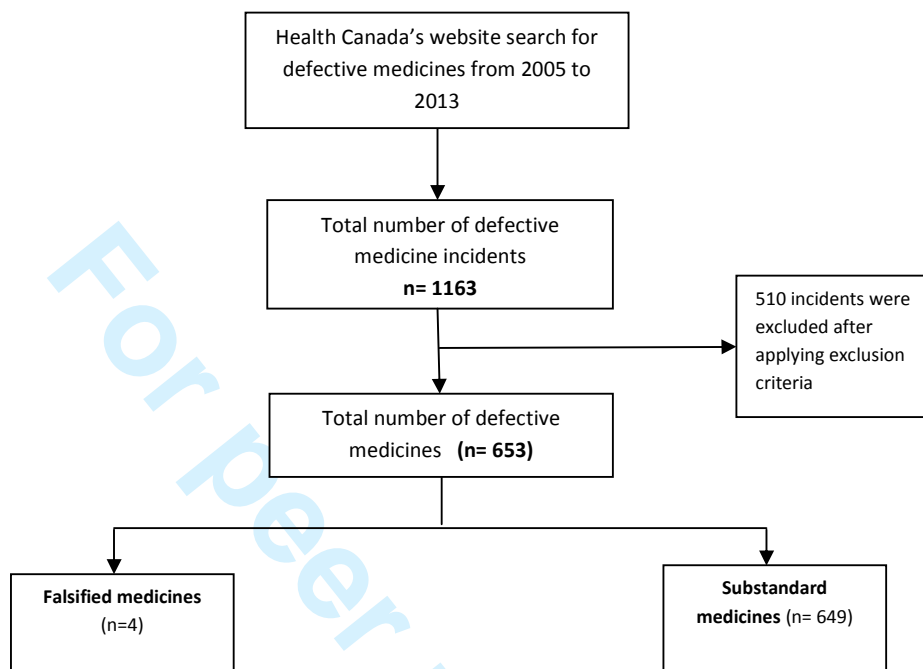
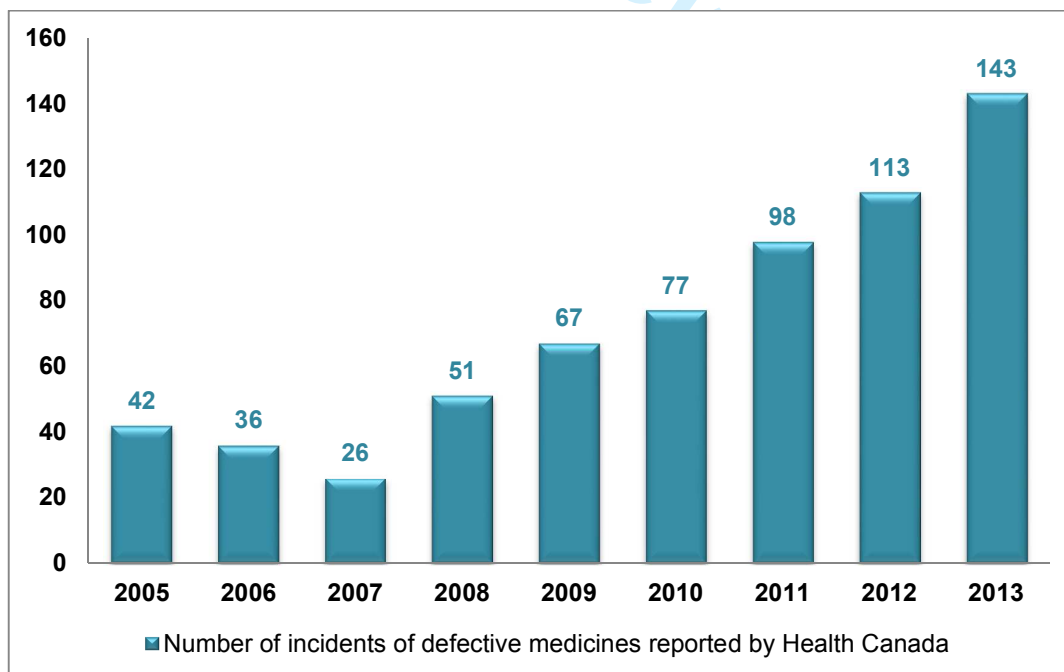
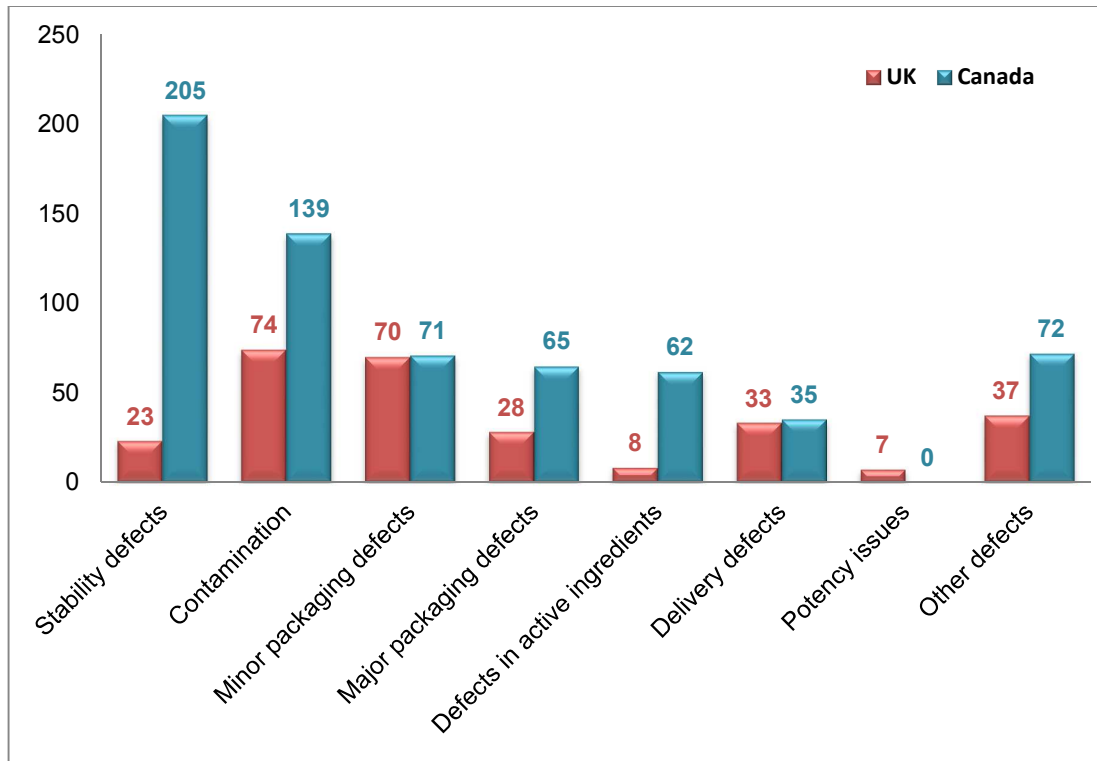


Figure 2: Number of incidents of defective medicines reported by Health Canada



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Figure 3: Comparison between Canada and the UK in the types of substandard medicines.



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Table 1: Substandard medicines

Defect Type	Number of medicines	%	Defect details	Number of medicines
Stability defects	205	32	Concern about stability of active ingredients	63
			Levels of impurities in excess of specification at different time points	50
			Dissolution, disintegration and drug release failure	45
			Others	47
Contamination	139	21	Impurities	82
			Lack of sterility assurance	35
			Microbial contamination	22
Minor packaging defects	71	11	Fault involving the external packaging or minor printing errors that do not involve name or strength of a medicines	60
			Missing or incorrect product registration number, batch number, manufacturer's name or expiry date	11
Major packaging defects	65	10	Missing or incorrect name ,strength, or active ingredient of a medicine on carton or box	35
			Packing a medicine in the wrong carton or present of a foreign tablet or capsule in the bottle or blister	30
Defects in active ingredient	62	10	Excessive amount of active ingredients	26
			Inadequate amount of active ingredient	20
			Active ingredient is out of specification	16
Delivery defects	35	5	Fault with a device	22
			Leakage or loose/ tight seal ,cracks in a vial or broken tablets	9
			Others	4
Other defects	72	11	GMP deficiencies and deviation from preapproved specifications	48
			Inappropriate shipment	14
			Dissolution / disintegration failure	10
Total	649	100		649

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Table 2: Contaminated medicines urgently recalled

Medications (number of incidents)	Formulation	Defect description
Marcaine (2), acyclovir (1), nitroglycerin (1), magnesium sulfate (1), dexamethasone sodium (1), vistide (1) and carboplatin (1)	Solution for injection	Visible particulates were identified in the formulation (such as white, metallic or glass particles.)
Propofol (4) and fat emulsion (1)	Emulsion for injection	
Extraneal (1) ciprofloxacin (1), carmustine (1), technetium Tc 99m (1) and liposomal amphotericin B (1)	Solution for injection	Microbial contamination (bacterial, fungal or viral contamination)
Docusate sodium (1)	Capsules	
Sucrose (1)	Oral liquid	
Benzalkonium chloride (1)	Topical Liquid	
Sodium Chloride (1) and dextrose (1)	Solution for injection	Integrity of the foil seal is compromised leading to potential contamination of the vial adapter
Dianeal (1), DTE technetium Tc 99m (1), electrolyte infusion (1) and dextrose (1)	Solution for injection	Lack of sterility assurance at the time of manufacture
Gen Teal Artificial Tears (1)	Ophthalmic Solution	
Heparin sodium (3)	Solution for injection	Contamination with heparin-like contaminant
Quetiapine (3)	Tablets	cross-contamination of trace amounts of clindamycin in quetiapine active pharmaceutical ingredient during the manufacturing process

Table 3: Substandard medicines urgently recalled with other defect types

Type of defect	Medications (number of incidents)	Formulation	Defect description
Major packaging defects (incorrect labelling)	Trazodone (1), amlodipine (1) and fluvoxamine (1)	Tablets	Some products contained the wrong medicines due to labelling errors (e.g., amlodipine instead of minocycline, minocycline instead of amlodipine, clonazepam instead of rifampicin and fluphenazine instead of Octreotide) or filling errors (e.g., nabilone instead of trazodone, ciprofloxacin instead of fluvoxamine, trazodone instead of nabilone, Isoproterenol instead of morphine and blue collyrium instead of prednisolone)
	Nabilone (1), minocycline (1) and rifampicin (1)	Capsules	
	Morphine sulphate (1) and octreotide acetate omega (1)	Solution for injection	
	Prednisolone (1)	Ophthalmic solution	
	Hemodialysis acid concentrates (1), remifentanil HCl (1), pamidronate disodium (1), tobramycin (1) and triamcinolone acetonide (1)	Solution for injection	Wrong strength , dosage or expiry date were printed on the packaging
	Sodium solysterene sulfonate (1)	Suspension	
	Acetaminophen (1)	Suppositories	
	Personnelle cold and flu tablets (2), acetylsalicylic acid (1), acetaminophen (1) and Personelle acid control (1)	Tablets	Important mandatory warning statement was missed on the external packaging
	Oral contraceptive pills (4)	Tablets	Additional placebo tablet was found in place of an active tablet in one blister pack raising the risk of unwanted pregnancy
	Ibuprofen (2)	Tablets	The label stated that the bottle had a child resistant cap, but the cap used was not child resistant.
Stability defects	Smallpox vaccine (1)	Solution for injection	Evidence of instability based on its appearance.
	Timolol (1)	Ophthalmic Solution	Active ingredient was out of specification after 12 month of production date
	Valproic acid (1)	Capsules	Disintegration test failure within the shelf life of the drug
	Amoxicillin (1)	Suspension	Out of specification assay result was obtained at various time points.
Active ingredients defects	Phenobarbital (1) and morphine SR (1)	Tablets	Oversized tablets were found raising the risk of overdose
	Acetylsalicylic acid (1)		Inadequate amount of active ingredient
	Delflex (1) and carmustine (1)	Solution for injection	Excessive amount of active ingredients
	Ethacrynic acid (1)		Inadequate amount of active ingredient
Delivery defects	Paliperidone palmitate (1), nutrinal (1), degarelix (1), caspofungin acetate (1), vancomycin (1) and argatroban (1)	Solution for injection	Cracks in the syringes or vials , or leaks from the bags were identified raising the risk of contamination
	Sumatriptan (1)		Pre-filled syringes were filled with needles that protruded through the needle shield
	Morphine sulphate (1)		Plunger friction with the vial may cause pump occlusion or delivery of inaccurate dose
	Cough and Cold syrup (9)	Syrup	The child-resistant feature of the bottle cap was not functioning properly
Other	Hypromellose (1)	lubricant eye gel	Non-compliance with Good manufacturing practices

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Supplementary data:**Table 1: Number of formulations under each defect type of substandard medicines**

Defect Type	Formulation type	Number of formulations
Stability defect	Tablets	89
	Parenteral	46
	Topical preparations	34
	Capsules	24
	Liquid preparations	12
Contamination	Parenteral	71
	Tablets	29
	Topical preparations	21
	Liquid preparations	11
	Capsules	7
Minor packaging defect	Tablets	39
	Parenteral	14
	Capsules	9
	Liquid preparations	5
	Topical preparations	4
Major packaging defects	Tablets	35
	Parenteral	13
	Capsules	11
	Topical preparations	6
Defect in active ingredient	Tablets	18
	Topical preparations	16
	Parenteral	13
	Liquid preparations	8
	Capsules	6
Delivery defect	Parenteral	11
	Liquid preparations	10
	Topical preparations	8
	Tablets	6
	Capsules	1
Other defects	Tablets	35
	Parenteral	20
	Topical preparations	11
	Liquid preparations	3
	Capsules	3
Total		649

Table 2: Defective medicines reported by Health Canada, classified according to the organ or system in which they act and according to the therapeutic subgroup they belong (Classification ATC) 2005-2013:

Category	No.	%	Category	No.	%
According to organ or system in which the drug acts			According to subgroup, therapeutic main group		
Nervous system	141	21.7	Analgesics Psycholeptics Psychoanaleptics Anaesthetics Antiepileptics Anti-parkinson drugs	65 26 18 15 13 4	10.0 4.0 2.8 2.3 2.0 0.6
Alimentary tract and metabolism	90	13.9	Drugs for acid related disorders Vitamins Mineral supplements Laxatives Drugs used in diabetes Drugs for constipation Stomatological preparations	25 22 16 12 9 3 3	3.9 3.4 2.5 1.8 1.4 0.5 0.5
Cardiovascular System	83	12.8	Antihypertensives Lipid modifying agents Cardiac therapy	50 24 9	7.7 3.7 1.4
Anti-infectives for systemic use	65	10.0	Antibacterials for systemic use Antimycotics for systemic use Immune sera and immunoglobulins Vaccines Antivirals for systemic use	38 8 8 6 5	5.9 1.2 1.2 0.9 0.8
Blood and blood forming organs	63	9.7	Blood substitutes and perfusion solutions Antithrombotic agents Antianemic preparations	30 19 14	4.6 2.9 2.2
Dermatologicals	46	7.1	Corticosteroids, dermatological preparations Other dermatological preparations Anti-acne preparations Antifungals for dermatological use	18 14 9 5	2.8 2.2 1.4 0.8
Respiratory system	31	4.8	Antihistamines for systemic use Cough and cold preparations Drugs for obstructive airway diseases Nasal preparations	11 11 7 2	1.7 1.7 1.1 0.3
Genito-urinary system and sex hormones	29	4.5	Sex hormones and modulators of the genital system Urologicals Gynecological anti-infectives and antiseptics	22 5 2	3.4 0.8 0.3
Antineoplastic and immunomodulating agents	28	4.3	Antineoplastic agents Immunosuppressants Immunostimulants Endocrine therapy	18 4 4 2	2.8 0.6 0.6 0.3
Various	26	4.0	Diagnostic radiopharmaceuticals All other therapeutic products Contrast media	20 4 2	3.1 0.6 0.3
Sensory organs	21	3.2	Ophthalmologicals Otolologicals	20 1	3.1 0.2
Musculo-skeletal system	18	2.8	Anti-inflammatory and antirheumatic products Drugs for treatment of bone diseases Muscle relaxants	11 6 1	1.7 0.9 0.2
Systemic hormonal preparations, excluding sex hormones and insulins	8	1.2	Pituitary and hypothalamic hormones and analogues Pancreatic hormones Pituitary and hypothalamic hormones and analogues	3 3 2	0.5 0.5 0.3
Total	649	100	Total	649	100

Table 3: Substandard medicines categorised by manufacturer and type of defects

Manufacturer	Number of medicines under each type of quality defect							Total	Total number of generic medicines produced by each manufacturer
	Substandard medicines								
	Stability	Contamination	Minor packaging	Active ingredient	Major packaging	Delivery	Others		
Apotex Inc.	31	13	4	2	2	2	3	57	220
Teva Canada Ltd.	15	11	5	7	10	2	3	53	224
Pharmascience Inc.	12	3	3	6	6	2	3	35	173
Vita Health Products Inc.	4	0	14	4	10	1	0	33	NA
Sandoz Canada Inc.	5	8	1	12	5	0	0	31	232
Hospira Healthcare Co.	1	13	0	0	0	3	9	26	94
Novartis Pharmaceuticals Canada Inc.	4	2	1	1	1	13	1	23	114
Pfizer Canada Inc.	10	2	4	1	1	1	1	20	120
GlaxoSmithKline Inc.	3	8	2	6	0	1	0	20	77
Baxter Co.	2	8	4	0	1	1	0	16	58
Sanofi-Aventis Canada Inc.	4	1	2	5	0	0	4	16	76
Laboratoire Riva Inc	11	1	0	0	0	0	1	13	NA
Mylan pharmaceuticals	0	0	2	1	4	1	3	11	145
Pharmetics Inc.	1	3	0	0	0	0	2	10	NA
JAMP Pharma Co.	4	1	1	3	0	0	1	10	37
Pharmaceutical Partners of Canada.	2	3	0	0	1	1	2	9	40
Schering-Plough Canada Inc.	3	1	2	0	0	0	2	8	72
McNeil Consumer Products Co.	0	2	1	0	0	0	5	8	28
								399	

BMJ Open

Quality of medicines in Canada: a retrospective review of risk communication documents (2005–2013)

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-006088.R1
Article Type:	Research
Date Submitted by the Author:	26-Aug-2014
Complete List of Authors:	Almuzaini, Tariq; University of Nottingham, Academic Division of Child Health Sammons, Helen; University of Nottingham, Child Health Choonara, Imti; University of Nottingham, Academic Division of Child Health
Primary Subject Heading:	Public health
Secondary Subject Heading:	Health policy, Pharmacology and therapeutics
Keywords:	Substandard medicines, Falsified medicines, Drug recalls

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3 **Quality of medicines in Canada: a retrospective review of risk**
4 **communication documents (2005–2013)**
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38
39 **Abstract:** 253 words
40

41 **Full text:** 3220 words
42

43 **Number of figures:** 3
44

45 **Number of tables:** 4
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47

48
49 **Keywords:** Falsified, substandard, defective, medicines, recalls
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ABSTRACT

Objective: To explore the quality and safety of medicines in Canada.

Design: A retrospective review of drug recalls and risk communication documents conveying issues relating to defective (i.e., substandard and falsified) medicines.

Setting: The Health Canada website search for drug recalls and risk communication documents issued between 2005 and 2013.

Eligibility criteria: Drug recalls and risk communication documents related to quality defect in medicinal products.

Main outcome measure: Relevant data about defective medicines reported in drug recalls and risk communication documents, including description of the defect, type of formulation, year of the recall and category of the recall or the document.

Results: There were 653 defective medicines of which 649 were substandard. The number of defective medicines reported by Health Canada increased from 42 in 2005 to 143 in 2013. The two most frequently reported types of defects were stability (205 incidents) and contamination issues (139 incidents). Some of these defects were found to be more prominent and repetitive over other types within some manufacturers. Tablet formulation (251 incidents) was the formulation most frequently compromised. No significant differences were observed between the manufacturers and distributors in the number of substandard medicines reported under each defect type. There were only four falsified medicines reported over the nine-year period.

Conclusions: Substandard medicines are an increasing problem in Canada and have resulted in a large number of recalled medicines. Most of the failures were related to stability issues, raising the need to investigate the root causes and for stringent preventative measures to be implemented by manufacturers.

Strengths and limitations of this study

- It is the first review to assess the problem of defective medicines in Canada.
- It quantifies and analyses drug recalls in Canada over a 9- year period.
- Clinical significance of the problem is undetermined, owing to the lack of data from Health Canada regarding adverse events associated with the use of defective medicines.

INTRODUCTION

Defective medicines are a major public health problem¹⁻⁴ Different surveys in lower income countries (LIC) and lower-middle-income countries (LMIC) have found that defective medicines are readily available.^{3, 5}

Defective medicine is a term used to describe any drug with a quality defect, whether the error was due to deliberate falsification or unintentional error during manufacturing.^{6, 7} It is a large category that comprises two main types of compromised drugs, substandard and falsified medicines. A substandard medicine is a medicine that does not meet the regulator standards due to an unintentional or negligent error.⁸ A falsified medicine, however, is one where deliberate and criminal intent is involved.⁸

In high income countries (HIC), there have been no studies with good methodological quality examining the overall prevalence of substandard or falsified medicines.³ HIC in Europe and North America, however, enjoy robust surveillance systems that have identified and withdrawn several medicines from the market with serious safety concerns.^{9, 10} These surveillance systems have reported numerous incidents of substandard and falsified medicines, and highlighted the problem of such drugs in these countries. Examples of these are the falsified cancer drug, Avastin, and substandard spinal steroid injections reported in the USA.^{11, 12} In our previous study on the UK, we studied the problem of defective medicines in the UK by reviewing the drug alerts issued by the drug regulator over an 11-year period. The study showed that substandard medicines are a significant problem that appears to be increasing.⁷ We wished to explore another HIC and chose Canada, as the problem of defective medicines has never been explored in this setting.

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3 In Canada, Health products are regulated by Health Canada, which is the federal
4 department responsible for the monitoring and regulating of medicines.¹³ It issues a
5 number of risk communication documents to the public and healthcare professionals.
6 These involve identification of the possible risk, assessment of its severity and
7 clarification of the nature of the problem. This communication is also initiated to
8 disseminate information regarding new safety issues of medicines or existing health
9 risks to allow healthcare professionals and their patients to make well-informed
10 decisions about their health.¹⁴

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17 The aim of this study was to explore the quality and safety of medicines in Canada by
18 analysing the risk communication documents conveying issues relating to defective
19 medicines.
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22 23 24 25 **METHODS**

26
27 Health Canada uses 13 risk communication documents, which can be issued for the
28 public, healthcare professionals, and hospitals.¹⁴ A preliminary search for these risk
29 communication documents found that only five documents can be used by Health
30 Canada to convey any defective health product issue in the Canadian official supply
31 chain. These can be described as follows:
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37 • **Public Warning (PW):** issued by Health Canada if the use of the drug can
38 cause a severe adverse health consequence that may lead to death.
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41 • **Public Advisory (PA):** issued by Health Canada if exposure to or the use of
42 the drug can cause adverse health consequences, but is not life threatening
43 or serious.
- 44
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46 • **Healthcare Professional Communication - Notice to Hospitals (HPC-
47 NtoH):** to inform the healthcare professional about time-sensitive issues
48 concerning safety and/or efficacy of medicinal products. It is intended for
49 hospital use only.
- 50
51
52 • **Healthcare Professional Communication - Dear Health Care Professional
53 Letter (HPC-DHCPL):** to inform the healthcare professional about issues
54 regarding safety and/or efficacy of medicinal products.
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- **Health Product Recall (with type I, II or III):** These can be classified according to the urgency of the recall as follows:
 - Health Product Recall type I: issued if the health product can cause severe adverse health consequence that may lead to death.
 - Health Product Recall type II: issued if the exposure to or the use of the health product can cause adverse health consequences but is not life threatening or serious.
 - Health Product Recall type III: The exposure to or use of the health product is not likely to cause any harm but the recall is initiated for other reasons such as minor deviation from specifications.

Both PW and Health Product Recall type I are considered by Health Canada to be urgent communications, as they are issued for a medicine which may pose a serious health risk. PA, HPC-NtoH, HPC-DHCPL and type II and III Health Product Recalls are semi-urgent communications where the risk associated with the use of a medicine is not serious.¹⁴

A search for risk communication documents conveying issues relating to defective medicines (i.e., substandard and falsified medicines) was carried out. This was performed through the official Health Canada's website and using the search engine allocated for advisories, warnings, and recalls of health products (<http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/index-eng.php>). Health Canada started posting Health Product Recalls on its website in 2005. These recalls are the main tool that Health Canada uses to convey quality issues with medicines. Before that, there were only two types of risk communication documents (PA and HPC-DHCPL) available on Health Canada's website. We wanted to examine the same documents throughout the years. Therefore, the search was started from 2005, and all risk communication documents issued between 2005 and 2013 were included. All risk communication documents (PW, PA, HPC-DHCPL, HPC-NtoH and Health Product Recalls) were reviewed and the relevant information was then extracted.

All relevant information regarding defective health products was compiled and exclusion criteria were as follows: veterinary medicines; medicines lacking efficacy; herbal and probiotic products; dietary and cosmetic products; and other natural

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3 health product recalled for regulatory reason (i.e., those do not have a valid
4 marketing authorisation). The following data were extracted from the risk
5 communication documents: name, strength, and dosage form; year of the document;
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7 nature of the defect; type of drug recall (in the case of Health Product Recalls); and
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9 action to be taken by healthcare professionals or the public regarding the defective
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11 medicine. In the case of Health Product Recalls and PW, the action is to remove the
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13 defective medicine from the dispensary shelves and contact the manufacturer for
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15 return. Whereas, with other risk communication documents where there is no recall
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17 required, healthcare professionals and the public are given advice on how to deal
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19 with defective medicines and to alert the public to be aware of expected risks. Two
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21 types of drugs can be distinguished from risk communication documents;
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23 substandard drugs and falsified drugs. The decision on which incident was falsified
24
25 or substandard is that published by Health Canada.

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27 The type of defects were then classified using the same classification as used in our
28
29 previous study.⁷ The quality defects were classified as contamination, minor or major
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31 packaging defect, delivery (e.g., leaking bags) defect, stability failure, potency
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33 issues, active ingredient defect and other issues (such as other deviations
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35 concerning non-compliance with good manufacturing practice at manufacturing site).

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37 The WHO Organization Anatomical Therapeutic Chemical (ATC) Classification
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39 System was used to classify defective medicines.¹⁵ The first level of this classification
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41 categorises medicines according to the organ or system in which they act and the
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43 second level classifies medicines according to their main therapeutic group. This
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45 was performed to highlight the most frequent therapeutic classes affected by these
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47 recalls.

48 49 **Method of analysis**

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51 Minitab (version 16) software was used to store and analyse the data. Descriptive
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53 statistics were used to summarise the results. Marketing authorisation holders of
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55 recalled medicines were either licensed manufacturers or distributors. A comparison
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57 between the manufacturers and distributors in the number of substandard medicines
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59 reported under each type of quality defect was carried out using Fisher's exact test.
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A significant difference was defined at P-value < 0.05.

RESULTS

A total of 653 defective medicines were identified in the Canadian supply chain (Figure 1). Among these defective medicines, 649 were found to be substandard medicines, and only four were found to be falsified medicines in the nine years studied. The rate of reporting defective medicines has increased each year over the last six years (Figure 2).

Substandard medicines

Substandard medicines represent the bulk of defective medicines ($n= 649$, 99%) reported by Health Canada. The two most frequent types of defects reported were stability ($n= 205$, 32%) and contamination ($n= 139$, 21%) issues (Table 1). It is clear that substandard medicines with stability defects represent the largest group. The majority of these formulations were found to have degraded one year after their release into the market, resulting in low concentrations of active ingredients, impurities, dissolution and disintegration failures. Tablets were the formulation most frequently reported to be substandard (supplementary table 1).

Among the 649 substandard medicines, 89 (14%) were subjected to urgent communications and therefore required urgent recalls. These medicines were reported using the Health Product Recall type 1 ($n= 87$) and the PW ($n=2$). More than half of these medicines ($n= 46$, 53%) were parenteral formulations (Tables 2 and 3). Of the 89 medicines that were recalled, 34 were contaminated. The majority of these were parenteral formulations that were recalled due to the presence of particulate matters, the presence of microbes, or a lack of sterility assurance during their manufacture (Table 2). The remaining substandard medicines ($n= 55$) were urgently recalled due to other types of defects (Table 3), mainly packaging defects or delivery issues (such as cracks in the vials or leaks in the bags, as well as faults in the unit used to deliver the medicines). Packaging defects were one of the major clinical issues reported, and these included incorrect labelling (i.e., wrong drug name, strength, or expiry date) and packaging that lacked important information regarding safety or the use of medicines in the patient information leaflets. In some cases, the labelling was correct, but the wrong medicines were filled, resulting in major and urgent recalls of affected batches (Table 3).

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3 Other substandard medicines ($n= 560$, 86%) were subjected to semi-urgent recalls
4 ($n= 536$) or caution in use ($n= 24$). These were reported via the Health Product
5 Recall type II ($n= 288$ medicines, 44%) and III ($n= 245$, 38%), PA ($n= 8$, 1%), HPC-
6 NtoH ($n= 9$, 1%) and HPC-DHCPL ($n= 7$, 1%). Three medicines were recalled, but
7 the corresponding type of Health Product Recall was not given by Health Canada.
8 The Majority of these drugs had stability, contamination and packaging defects
9 (supplementary table 2).
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15 Drugs that act on the nervous system ($n= 141$, 22%), alimentary tract and
16 metabolism ($n= 90$, 14%), and cardiovascular system ($n= 83$, 13%) were the
17 subgroups that most frequently contained substandard medicines. When the second
18 level of this classification (i.e., therapeutic classification) was used, the top three
19 groups reported to be substandard were analgesics ($n= 65$, 10%), antihypertensives
20 ($n= 50$, 8%) and antibacterials ($n= 38$, 6%) (supplementary table 3).
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29 **Substandard medicines categorised by manufacturers**

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31 The review identified 122 licensed manufacturers and 26 licensed distributors.
32 Manufacturers held the marketing authorisation for 611 substandard medicines and
33 distributors for 38 (Table 4). No unlicensed manufacturers or distributors were
34 involved. A comparison between those manufacturers and distributors in the number
35 of substandard medicines reported under each defect type revealed no significant
36 differences (Table 4).
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42 The top 20 manufacturers are listed in supplementary table 4. It was noted that 50%
43 or more of substandard medicines manufactured by Apotex Inc., Pfizer Canada Inc.
44 and Laboratoire Riva Inc. had stability issues. Almost half of the substandard
45 products from Baxter Co., Hospira Healthcare Co. and GlaxoSmithKline Inc. were
46 contaminated. Products of Sandoz Canada Inc. had a problem with the active
47 ingredient, which was either too high or too low. More than half of Novartis products,
48 which are reported to be substandard, were recalled due to delivery concerns, such
49 as failure of the child-resistant feature of the bottle cap or leaks in the infusion bags.
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Falsified medicines

Four incidents of falsified medicines were identified in Canada's supply chain between 2011 and 2013. All these incidents involved two sexual enhancement medicines, Viagra® (sildenafil) and Cialis® (tadalafil).

In all cases of falsified medicines, Public Advisories were issued to inform the public to contact their healthcare professionals if they had concerns about these falsified medicines. The public was also advised to verify that these products were assessed by Health Canada for safety by looking at the authorisation number printed on the label. These medicines were seized in the retail outlets in Canada, and no further information was given by Health Canada about the subsequent investigation or action taken by Health Canada.

DISCUSSION

This is the first review that discusses the issue of substandard and falsified medicines in Canada by evaluating the risk communication documents and drug recalls posted on Health Canada website. Our observations of defective medicines recalls over nine consecutive years, from 2005 to 2013, have shown that the recall of substandard medicines is an increasing trend. It is concerning that over half of the stability failures were related to instability of active ingredients or dissolution and disintegration failure. Both defects have the potential to affect the bioavailability of the active ingredients in the systemic circulation, and in turn, may lead to therapeutic failure.

Substandard medicines

The most frequent type of formulation reported to be substandard were tablets. Tablets have a slow onset of action and require less precaution in terms of sterility, than parenteral formulations. The extent of adverse consequences that can arise from failure to comply with manufacturing requirements, however, cannot be ignored. This was evident from the death of 120 patients in Pakistan due to contamination of isosorbide mononitrate tablets with large doses of an antimalarial drug.¹⁶ Another of the most pronounced examples is the phenobarbital and morphine tablet recalls in

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3 Canada. Oversized tablets (i.e. tablets that exceed the weight requirement) were
4 found in both drugs, raising the risk of the patients having as much as double the
5 strength stated on the bottle (Table 3). The Institute for Safe Medication Practices
6 (ISMP), a non-profit organisation, stated that the US manufacturer (KV
7 Pharmaceutical) received abnormally high reports of serious adverse events
8 concerning overdose.¹⁷ Adverse events relating to this defect have not been
9 documented by Health Canada.
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15 It was uncertain whether the rise of substandard medicines incidents were related to
16 improved detection by Health Canada or due to an increase of substandard medicine
17 production by manufacturers. The rate of increased incidence of substandard
18 medicines can be correlated with the implementation of improved detection policies
19 and regulations by Health Canada. Introduction of Good Manufacturing Practices
20 (GMP) inspection policy for Canadian drug establishments may be one of the
21 explanations.¹⁸ In January 2008, Health Canada introduced this policy as a response
22 to increasing demand to update its policy on GMP, given that so many GMP
23 guidelines and international agreements had been made since 1996. Subsequently,
24 there has been a steady increase of incidents of substandard medicines from 2008
25 to 2013 (Figure 2). This policy illustrates the procedures that the Health Products
26 and Food Branch (HPFB) follows to ensure that manufacturing sites, distributors and
27 wholesalers are complying with GMP. It is conducted via inspections by the HPFB
28 inspectorate with varying cycles, which depend on an approach that takes risk
29 assessment into consideration, and a ranking scale of priority.¹⁸ Similarly, it has been
30 highlighted that most of the FDA recalls were related to FDA inspectors' visits in the
31 USA.¹⁹
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45 **Manufacturing errors and investigation of the root cause**

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47 It is the responsibility of the manufacturers and marketing authorisation holders to recall
48 their substandard products after consultation with Health Canada. The majority of these
49 recalls were issued by the manufacturers or marketing authorisation holders using the
50 Health Product Recall type I, II and III, which accounted for 95% of the total
51 substandard medicines reported. Stability issues were mainly identified by the
52 manufacturers during on-going stability testing. However, it is unknown whether these
53 defects were identified by internal auditing systems of the manufacturers, by
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3 intervention of the Health Canada inspection team or by reports from healthcare
4 professionals.
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7 Analysing pharmaceutical product recalls can be of great importance to identify the root
8 causes of recalled medicines. The prompting of a drug recall can be regarded as a
9 disastrous failure of the manufacturer's quality plan. Even with stringent quality
10 measures, errors can occur.^{20, 21} Thus, it is very important to identify the root cause of
11 the defects to avoid similar episodes in the future. It has been highlighted in this review
12 that stability failure and contamination issues were the defect types being reported
13 most frequently. These issues affected several manufacturers on more than one
14 occasion (supplementary table 4). This highlights the need for root cause investigations
15 and appropriate measures to be implemented by manufacturers.
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22 **Falsified medicines**

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24 Only four incidents of falsified medicines were reported by Health Canada. The
25 detection is extremely low compared with substandard medicine. Health Canada has
26 robust GMP inspections that cover all drug establishments including manufacturers,
27 distributors and wholesalers. The reporting system of Health Canada is concerned
28 with falsified medicines detected within the scope of GMP inspections.¹⁸ Some
29 falsified medicines may be intercepted and seized by enforcement bodies on their
30 way to target destinations, but not necessarily intended for the Canadian market.
31 This may explain the low detection rate by Health Canada.
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39 **Comparison with the UK**

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41 Canada and the UK are two of the top pharmaceutical markets in the world, holding
42 equal global pharmaceutical market share values of USD \$21,877 and USD \$21,635
43 billion, respectively.²² They also use similar approaches in dealing with substandard
44 medicines based on the expected risk. In the UK, the drug regulator uses four
45 classes of drug alerts to communicate the risk of substandard medicines to
46 Healthcare professionals.⁶ A request to recall the affected batches is issued with the
47 first three classes (class 1-3 drug alerts), comparable to the Health Product recall
48 type I, II and III issued by Health Canada. A class 4 drug alert is issued by the UK
49 drug regulator when a drug recall is not required, but caution is needed to deal with a
50 substandard medicine. This type of communication is similar to the PA, HPC-NtoH
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3 and HPC-DHCPL used by Health Canada. A class 1 drug recall (issued in the UK),
4 and both the Health Product recall type I and PW (issued in Canada) are considered
5 to be urgent communications. The rest of the documents in both countries are
6 deemed as semi-urgent communications.^{6, 14}
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10 Out of the 280 substandard medicines found in the UK, 17 (6%) were subject to
11 urgent communication.⁷ The corresponding number in Canada was 89 (13%) out of
12 649. Overall, a larger number of substandard medicines were found in the Canadian
13 supply chain (649 medicines) than in the UK (280 medicines).⁷ The major contributor
14 to this difference in our data was the number of medicines recalled due to stability
15 problems (Figure 3), which were responsible for 50% of the difference. The
16 differences in stability issues between Canada and the UK require further
17 investigation.
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24 **Limitations**

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27 This study encountered some limitations. Firstly, the expected adverse events
28 associated with the use of substandard medicines were not reported by Health
29 Canada or the manufacturers. Moreover, the adverse reaction database does not
30 state the batch numbers of medicines reported with the complaint. Therefore we
31 could not compare the expected risk associated with the recalled batches of
32 substandard medicines with the adverse drug reaction database. Thus, the clinical
33 significance of the problem is unknown.
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42 **CONCLUSION**

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44 Substandard medicines are an increasing problem in Canada and have resulted in a
45 large number of recalled medicines. Most of the failures were related to stability
46 issues, raising the need to investigate the root causes and for stringent preventative
47 measures to be implemented by manufacturers. Regular GMP inspections on
48 manufacturing sites were highlighted in this review as some of the most important
49 tools that can improve detection of substandard medicines.
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Contributors:

TA and IC conceived the study design and planned the research. TA performed the database search, extracted the data and drafted the manuscript. HS double-checked the extracted data, and interpreted the results. IC and HS edited and reviewed the manuscript. All authors approved the final version of the manuscript.

Competing interests: None.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Ethical approval: Not required.

Data sharing: No additional data available.

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TABLES:

Table 1: Substandard medicines

Defect Type	Number of medicines	%	Defect details	Number of medicines
Stability defects	205	32	Concern about stability of active ingredients	63
			Levels of impurities in excess of specification at different time points	50
			Dissolution, disintegration and drug release failure	45
			Others	47
Contamination	139	21	Impurities	82
			Lack of sterility assurance	35
			Microbial contamination	22
Minor packaging defects	71	11	Fault involving the external packaging or minor printing errors that do not involve name or strength of a medicines	60
			Missing or incorrect product registration number, batch number, manufacturer's name or expiry date	11
Major packaging defects	65	10	Missing or incorrect name ,strength, or active ingredient of a medicine on carton or box	35
			Packing a medicine in the wrong carton or present of a foreign tablet or capsule in the bottle or blister	30
Defects in active ingredient	62	10	Excessive amount of active ingredients	26
			Inadequate amount of active ingredient	20
			Active ingredient is out of specification	16
Delivery defects	35	5	Fault with a device	22
			Leakage or loose/ tight seal ,cracks in a vial or broken tablets	9
			Others	4
Other defects	72	11	GMP deficiencies and deviation from preapproved specifications	48
			Inappropriate shipment	14
			Dissolution / disintegration failure	10
Total	649	100		649

Table 2: Contaminated medicines subjected to urgent recalls (Health Product Recall type I).

Medications (number of incidents)	Formulation	Defect description
Marcaine (2), acyclovir (1), nitroglycerin (1), magnesium sulfate (1), dexamethasone sodium (1), vistide (1) and carboplatin (1)	Solution for injection	Visible particulates were identified in the formulation (such as white, metallic or glass particles.)
Propofol (4) and fat emulsion (1)	Emulsion for injection	
Extraneal (1) ciprofloxacin (1), carmustine (1), technetium Tc 99m (1) and liposomal amphotericin B (1)	Solution for injection	Microbial contamination (bacterial, fungal or viral contamination)
Docusate sodium (1)	Capsules	
Sucrose (1)	Oral liquid	
Benzalkonium chloride (1)	Topical Liquid	
Sodium Chloride (1) and dextrose (1)	Solution for injection	Integrity of the foil seal is compromised leading to potential contamination of the vial adapter
Diameal (1), DTE technetium Tc 99m (1), electrolyte infusion (1) and dextrose (1)	Solution for injection	Lack of sterility assurance at the time of manufacture
Gen Teal Artificial Tears (1)	Ophthalmic Solution	
Heparin sodium (3)	Solution for injection	Contamination with heparin-like contaminant
Quetiapine (3)	Tablets	cross-contamination of trace amounts of clindamycin in quetiapine active pharmaceutical ingredient during the manufacturing process

Note: All medicines were reported using health Product Recall Type I document

Table 3: Substandard medicines subjected to urgent recalls (Health Product Recall type I and PW) with other defect types

Type of defect	Medications (number of incidents)	Formulation	Defect description
Major packaging defects (incorrect labelling)	Trazodone (1), amlodipine (1) and fluvoxamine (1)	Tablets	Some products contained the wrong medicines due to labelling errors (e.g., amlodipine instead of minocycline, minocycline instead of amlodipine, clonazepam instead of rifampicin and fluphenazine instead of Octreotide) or filling errors (e.g., nabilone instead of trazodone, ciprofloxacin instead of fluvoxamine, trazodone instead of nabilone, Isoproterenol instead of morphine and blue collyrium instead of prednisolone)
	Nabilone (1), minocycline (1) and rifampicin (1)	Capsules	
	Morphine sulphate (1) and octreotide acetate omega (1)	Solution for injection	
	Prednisolone (1)*	Ophthalmic solution	
	Hemodialysis acid concentrates (1), remifentanil HCl (1), pamidronate disodium (1), tobramycin (1) and triamcinolone acetonide (1)	Solution for injection	Wrong strength , dosage or expiry date were printed on the packaging
	Sodium solysterene sulfonate (1)	Suspension	
	Acetaminophen (1)	Suppositories	
	Personnelle cold and flu tablets (2), acetylsalicylic acid (1), acetaminophen (1) and Personelle acid control (1)	Tablets	Important mandatory warning statement was missed on the external packaging
	Oral contraceptive pills (4)	Tablets	Additional placebo tablet was found in place of an active tablet in one blister pack raising the risk of unwanted pregnancy
Ibuprofen (2)	Tablets	The label stated that the bottle had a child resistant cap, but the cap used was not child resistant.	
Stability defects	Smallpox vaccine (1)	Solution for injection	Evidence of instability based on its appearance.
	Timolol (1)	Ophthalmic Solution	Active ingredient was out of specification after 12 month of production date
	Valproic acid (1)	Capsules	Disintegration test failure within the shelf life of the drug
	Amoxicillin (1)	Suspension	Out of specification assay result was obtained at various time points.
Active ingredients defects	Phenobarbital (1)* and morphine SR (1)	Tablets	Oversized tablets were found raising the risk of overdose
	Acetylsalicylic acid (1)		Inadequate amount of active ingredient
	Delflex (1)and carmustine (1)	Solution for injection	Excessive amount of active ingredients
	Ethacrynic acid (1)		Inadequate amount of active ingredient
Delivery defects	Paliperidone palmitate (1), nutrinal (1), degarelix (1), caspofungin acetate (1), vancomycin (1) and argatroban (1)	Solution for injection	Cracks in the syringes or vials , or leaks from the bags were identified raising the risk of contamination
	Sumatriptan (1)		Pre-filled syringes were filled with needles that protruded through the needle shield
	Morphine sulphate (1)		Plunger friction with the vial may cause pump occlusion or delivery of inaccurate dose
	Cough and Cold syrup (9)	Syrup	The child-resistant feature of the bottle cap was not functioning properly
Other	Hypromellose (1)	lubricant eye gel	Non-compliance with Good manufacturing practices

*Medicine was reported using the Public Warning document. Others were reported using Health Product Recall type I

Table 4: Substandard medicines categorised by the type of the Marketing Authorisation Holders

Type of quality defect	Medicines marketed by manufacturers (n= 122)	Medicines marketed by distributors (n= 26)	P-Value*
	Number of medicines, (%)	Number of medicines, (%)	
Stability	191 (31)	14 (37)	0.476
Contamination	134 (22)	5 (13)	0.228
Minor packaging	69 (11)	2 (5)	0.417
Major packaging	60 (10)	5 (13)	0.573
Active ingredient	59 (10)	3 (8)	1.000
Delivery	34 (5)	1 (3)	0.714
Others	64 (11)	8 (21)	0.058
Total	611 (100)	38 (100)	

*A significant difference was defined at a p value <0.05.

Figure legends:

Figure 1: Flow diagram of search and resulting incidents.

Figure 2: Number of incidents of defective medicines reported by Health Canada.

Figure 3: Comparison between Canada and the UK in the types of substandard medicines.

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3 **Quality of medicines in Canada: a retrospective review of risk**
4 **communication documents (2005–2013)**
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ABSTRACT

Objective: To explore [the quality and safety of medicines](#) in Canada.

Design: [A retrospective review of drug recalls and risk communication documents conveying issues relating to defective \(i.e., substandard and falsified\) medicines.](#)

Setting: The Health Canada website search for drug recalls and risk communication documents issued between 2005 and 2013.

Eligibility criteria: Drug recalls and risk communication documents related to quality defect in medicinal products.

Main outcome measure: Relevant data about defective medicines reported in drug recalls and risk communication documents, including description of the defect, type of formulation, year of the recall and category of the recall or the document.

Results: There were 653 defective medicines of which 649 were substandard. The number of defective medicines reported by Health Canada increased from 42 in 2005 to 143 in 2013. The two most frequently reported types of defects were stability (205 incidents) and contamination issues (139 incidents). Some of these defects were found to be more prominent and repetitive over other types within some manufacturers. Tablet formulation (251 incidents) was the formulation most frequently compromised. [No significant differences were observed between the manufacturers and distributors in the number of substandard medicines reported under each defect type.](#) There were [only](#) four falsified medicines reported over the nine-year period.

Conclusions: Substandard medicines are [an increasing](#) problem in Canada and have resulted in a large number of recalled medicines. Most of the failures were related to stability issues, raising the need to investigate the root causes and for stringent preventative measures to be implemented by manufacturers.

Strengths and limitations of this study

- It is the first review to assess the problem of defective medicines in Canada.
- It quantifies and analyses drug recalls in Canada over a 9- year period.
- Clinical significance of the problem is undetermined, owing to the lack of data from Health Canada regarding adverse events associated with the use of defective medicines.

INTRODUCTION

Defective medicines are a major public health problem¹⁻⁴ Different surveys in lower income countries (LIC) and lower-middle-income countries (LMIC) have found that defective medicines are readily available.^{3, 5}

Defective medicine is a term used to describe any drug with a quality defect, whether the error was due to deliberate falsification or unintentional error during manufacturing.^{6, 7} It is a large category that comprises two main types of compromised drugs, substandard and falsified medicines. A substandard medicine is a medicine that does not meet the regulator standards due to an unintentional or negligent error.⁸ A falsified medicine, however, is one where deliberate and criminal intent is involved.⁸

In high income countries (HIC), there have been no studies with good methodological quality examining the overall prevalence of substandard or falsified medicines.³ HIC in Europe and North America, however, enjoy robust surveillance systems that have identified and withdrawn several medicines from the market with serious safety concerns.^{9, 10} These surveillance systems have reported numerous incidents of substandard and falsified medicines, and highlighted the problem of such drugs in these countries. Examples of these are the falsified cancer drug, Avastin, and substandard spinal steroid injections reported in the USA.^{11, 12} In our previous study on the UK, we studied the problem of defective medicines in the UK by reviewing the drug alerts issued by the drug regulator over an 11-year period. The study showed that substandard medicines are a significant problem that appears to be increasing.⁷ We wished to explore another HIC and chose Canada, as the problem of defective medicines has never been explored in this setting.

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3 In Canada, Health products are regulated by Health Canada, which is the federal
4 department responsible for the monitoring and regulating of medicines.¹³ It issues a
5 number of risk communication documents to the public and healthcare professionals.
6 These involve identification of the possible risk, assessment of its severity and
7 clarification of the nature of the problem. This communication is also initiated to
8 disseminate information regarding new safety issues of medicines or existing health
9 risks to allow healthcare professionals and their patients to make well-informed
10 decisions about their health.¹⁴

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17 The aim of this study was to explore the quality and safety of medicines in Canada by
18 analysing the risk communication documents conveying issues relating to defective
19 medicines.
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25 METHODS

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27 Health Canada uses 13 risk communication documents, which can be issued for the
28 public, healthcare professionals, and hospitals.¹⁴ A preliminary search for these risk
29 communication documents found that only five documents can be used by Health
30 Canada to convey any defective health product issue in the Canadian official supply
31 chain. These can be described as follows:
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37 • **Public Warning (PW):** issued by Health Canada if the use of the drug can
38 cause a severe adverse health consequence that may lead to death.
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40 • **Public Advisory (PA):** issued by Health Canada if exposure to or the use of
41 the drug can cause adverse health consequences, but is not life threatening
42 or serious.
- 43
44 • **Healthcare Professional Communication - Notice to Hospitals (HPC-
45 NtoH):** to inform the healthcare professional about time-sensitive issues
46 concerning safety and/or efficacy of medicinal products. It is intended for
47 hospital use only.
- 48
49 • **Healthcare Professional Communication - Dear Health Care Professional
50 Letter (HPC-DHCPL):** to inform the healthcare professional about issues
51 regarding safety and/or efficacy of medicinal products.
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- **Health Product Recall (with type I, II or III):** These can be classified according to the urgency of the recall as follows:
 - Health Product Recall type I: issued if the health product can cause severe adverse health consequence that may lead to death.
 - Health Product Recall type II: issued if the exposure to or the use of the health product can cause adverse health consequences but is not life threatening or serious.
 - Health Product Recall type III: The exposure to or use of the health product is not likely to cause any harm but the recall is initiated for other reasons such as minor deviation from specifications.

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Both PW and Health Product Recall type I are considered by Health Canada to be urgent communications, as they are issued for a medicine which may pose a serious health risk. PA, HPC-NtoH, HPC-DHCPL and type II and III Health Product Recalls are semi-urgent communications where the risk associated with the use of a medicine is not serious.¹⁴

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A search for risk communication documents conveying issues relating to defective medicines (i.e., substandard and falsified medicines) was carried out. This was performed through the official Health Canada's website and using the search engine allocated for advisories, warnings, and recalls of health products (<http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/index-eng.php>). Health Canada started posting Health Product Recalls on its website in 2005. These recalls are the main tool that Health Canada uses to convey quality issues with medicines. Before that, there were only two types of risk communication documents (PA and HPC-DHCPL) available on Health Canada's website. We wanted to examine the same documents throughout the years. Therefore, the search was started from 2005, and all risk communication documents issued between 2005 and 2013 were included. All risk communication documents (PW, PA, HPC-DHCPL, HPC-NtoH and Health Product Recalls) were reviewed and the relevant information was then extracted.

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All relevant information regarding defective health products was compiled and exclusion criteria were as follows: veterinary medicines; medicines lacking efficacy; herbal and probiotic products; dietary and cosmetic products; and other natural

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3 health product recalled for regulatory reason (i.e., those do not have a valid
4 marketing authorisation). The following data were extracted from the risk
5 communication documents: name, strength, and dosage form; year of the document;
6 nature of the defect; type of drug recall (in the case of Health Product Recalls); and
7 action to be taken by healthcare professionals or the public regarding the defective
8 medicine. In the case of Health Product Recalls and PW, the action is to remove the
9 defective medicine from the dispensary shelves and contact the manufacturer for
10 return. Whereas, with other risk communication documents where there is no recall
11 required, healthcare professionals and the public are given advice on how to deal
12 with defective medicines and to alert the public to be aware of expected risks. Two
13 types of drugs can be distinguished from risk communication documents;
14 substandard drugs and falsified drugs. The decision on which incident was falsified
15 or substandard is that published by Health Canada.

16
17 The type of defects were then classified using the same classification as used in our
18 previous study.⁷ The quality defects were classified as contamination, minor or major
19 packaging defect, delivery (e.g., leaking bags) defect, stability failure, potency
20 issues, active ingredient defect and other issues (such as other deviations
21 concerning non-compliance with good manufacturing practice at manufacturing site).

22
23 The WHO Organization Anatomical Therapeutic Chemical (ATC) Classification
24 System was used to classify defective medicines.¹⁵ The first level of this classification
25 categorises medicines according to the organ or system in which they act and the
26 second level classifies medicines according to their main therapeutic group. This
27 was performed to highlight the most frequent therapeutic classes affected by these
28 recalls.

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Method of analysis

Minitab (version 16) software was used to store and analyse the data. Descriptive statistics were used to summarise the results. Marketing authorisation holders of recalled medicines were either licensed manufacturers or distributors. A comparison between the manufacturers and distributors in the number of substandard medicines reported under each type of quality defect was carried out using Fisher's exact test. A significant difference was defined at P-value < 0.05.

RESULTS

A total of 653 defective medicines were identified in the Canadian supply chain (Figure 1). Among these defective medicines, 649 were found to be substandard medicines, and only four were found to be falsified medicines in the nine years studied. The rate of reporting defective medicines has increased each year over the last six years (Figure 2).

Substandard medicines

Substandard medicines represent the bulk of defective medicines ($n= 649$, 99%) reported by Health Canada. The two most frequent types of defects reported were stability ($n= 205$, 32%) and contamination ($n= 139$, 21%) issues (Table 1). It is clear that substandard medicines with stability defects represent the largest group. The majority of these formulations were found to have degraded one year after their release into the market, resulting in low concentrations of active ingredients, impurities, dissolution and disintegration failures. Tablets were the formulation most frequently reported to be substandard (supplementary table 1).

Among the 649 substandard medicines, 89 (14%) were subjected to urgent communications and therefore required urgent recalls. These medicines were reported using the Health Product Recall type 1 ($n= 87$) and the PW ($n=2$). More than half of these medicines ($n= 46$, 53%) were parenteral formulations (Tables 2 and 3). Of the 89 medicines that were recalled, 34 were contaminated. The majority of these were parenteral formulations that were recalled due to the presence of particulate matters, the presence of microbes, or a lack of sterility assurance during their manufacture (Table 2). The remaining substandard medicines ($n= 55$) were urgently recalled due to other types of defects (Table 3), mainly packaging defects or delivery issues (such as cracks in the vials or leaks in the bags, as well as faults in the unit used to deliver the medicines). Packaging defects were one of the major clinical issues reported, and these included incorrect labelling (i.e., wrong drug name, strength, or expiry date) and packaging that lacked important information regarding safety or the use of medicines in the patient information leaflets. In some cases, the labelling was correct, but the wrong medicines were filled, resulting in major and urgent recalls of affected batches (Table 3).

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3 Other substandard medicines ($n= 560$, 86%) were subjected to semi-urgent recalls
4 ($n= 536$) or caution in use ($n= 24$). These were reported via the Health Product
5 Recall type II ($n= 288$ medicines, 44%) and III ($n= 245$, 38%), PA ($n= 8$, 1%), HPC-
6 NtoH ($n= 9$, 1%) and HPC-DHCPL ($n= 7$, 1%). Three medicines were recalled, but
7 the corresponding type of Health Product Recall was not given by Health Canada.
8 The Majority of these drugs had stability, contamination and packaging defects
9 (supplementary table 2).
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Drugs that act on the nervous system ($n= 141$, 22%), alimentary tract and metabolism ($n= 90$, 14%), and cardiovascular system ($n= 83$, 13%) were the subgroups that most frequently contained substandard medicines. When the second level of this classification (i.e., therapeutic classification) was used, the top three groups reported to be substandard were analgesics ($n= 65$, 10%), antihypertensives ($n= 50$, 8%) and antibacterials ($n= 38$, 6%) (supplementary table 3).

Substandard medicines categorised by manufacturers

The review identified 122 licensed manufacturers and 26 licensed distributors. Manufacturers held the marketing authorisation for 611 substandard medicines and distributors for 38 (Table 4). No unlicensed manufacturers or distributors were involved. A comparison between those manufacturers and distributors in the number of substandard medicines reported under each defect type revealed no significant differences (Table 4).

The top 20 manufacturers are listed in supplementary table 4. It was noted that 50% or more of substandard medicines manufactured by Apotex Inc., Pfizer Canada Inc. and Laboratoire Riva Inc. had stability issues. Almost half of the substandard products from Baxter Co., Hospira Healthcare Co. and GlaxoSmithKline Inc. were contaminated. Products of Sandoz Canada Inc. had a problem with the active ingredient, which was either too high or too low. More than half of Novartis products, which are reported to be substandard, were recalled due to delivery concerns, such as failure of the child-resistant feature of the bottle cap or leaks in the infusion bags.

Falsified medicines

Four incidents of falsified medicines were identified in Canada's supply chain between 2011 and 2013. All these incidents involved two sexual enhancement medicines, Viagra® (sildenafil) and Cialis® (tadalafil).

In all cases of falsified medicines, Public Advisories were issued to inform the public to contact their healthcare professionals if they had concerns about these falsified medicines. The public was also advised to verify that these products were assessed by Health Canada for safety by looking at the authorisation number printed on the label. These medicines were seized in the retail outlets in Canada, and no further information was given by Health Canada about the subsequent investigation or action taken by Health Canada.

DISCUSSION

This is the first review that discusses the issue of substandard and falsified medicines in Canada by evaluating the risk communication documents and drug recalls posted on Health Canada website. Our observations of defective medicines recalls over nine consecutive years, from 2005 to 2013, have shown that the recall of substandard medicines is an increasing trend. It is concerning that over half of the stability failures were related to instability of active ingredients or dissolution and disintegration failure. Both defects have the potential to affect the bioavailability of the active ingredients in the systemic circulation, and in turn, may lead to therapeutic failure.

Substandard medicines

The most frequent type of formulation reported to be substandard were tablets. Tablets have a slow onset of action and require less precaution in terms of sterility, than parenteral formulations. The extent of adverse consequences that can arise from failure to comply with manufacturing requirements, however, cannot be ignored. This was evident from the death of 120 patients in Pakistan due to contamination of isosorbide mononitrate tablets with large doses of an antimalarial drug.¹⁶ Another of the most pronounced examples is the phenobarbital and morphine tablet recalls in

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3 Canada. Oversized tablets (i.e. tablets that exceed the weight requirement) were
4 found in both drugs, raising the risk of the patients **having** as much as double the
5 strength stated on the bottle (Table 3). The Institute for Safe Medication Practices
6 (ISMP), a non-profit organisation, stated that the US manufacturer (KV
7 Pharmaceutical) received abnormally high reports of serious adverse events
8 concerning overdose.¹⁷ Adverse events relating to this defect have not been
9 documented by Health Canada.
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15 It was uncertain whether the rise of substandard medicines incidents were related to
16 improved detection by Health Canada or due to an increase of substandard medicine
17 production by manufacturers. The rate of increased incidence of substandard
18 medicines can be correlated with the implementation of improved detection policies
19 and regulations by Health Canada. Introduction of **Good Manufacturing Practices**
20 (GMP) inspection policy for Canadian drug establishments may be one of the
21 explanations.¹⁸ In January 2008, Health Canada introduced this policy as a response
22 to increasing demand to update its policy on GMP, given that so many GMP
23 guidelines and international agreements had been made since 1996. Subsequently,
24 there has been a steady increase of incidents of substandard medicines from 2008
25 to 2013 (Figure 2). This policy illustrates the procedures that the Health Products
26 and Food Branch (HPFB) follows to ensure that manufacturing sites, distributors and
27 wholesalers are complying with GMP. It is conducted via inspections by the HPFB
28 inspectorate with varying cycles, which depend on an approach that takes risk
29 assessment into consideration, and a ranking scale of priority.¹⁸ Similarly, it has been
30 highlighted that most of the FDA recalls were related to FDA inspectors' visits in the
31 USA.¹⁹
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45 **Manufacturing errors and investigation of the root cause**

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47 It is the responsibility of the manufacturers and marketing authorisation holders to recall
48 their substandard products after consultation with Health Canada. The majority of these
49 recalls were issued by the manufacturers or marketing authorisation holders using the
50 Health Product Recall type I, II and III, which accounted for 95% of the total
51 substandard medicines reported. Stability issues were mainly identified by the
52 manufacturers during on-going stability testing. However, it is unknown whether these
53 defects were identified by internal auditing systems of the manufacturers, by
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3 intervention of the Health Canada inspection team or by reports from healthcare
4 professionals.
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7 Analysing pharmaceutical product recalls can be of great importance to identify the root
8 causes of recalled medicines. The prompting of a drug recall can be regarded as a
9 disastrous failure of the manufacturer's quality plan. Even with stringent quality
10 measures, errors can occur.^{20, 21} Thus, it is very important to identify the root cause of
11 the defects to avoid similar episodes in the future. It has been highlighted in this review
12 that stability failure and contamination issues were the defect types being reported
13 most frequently. These issues affected several manufacturers on more than one
14 occasion (supplementary table 4). This highlights the need for root cause investigations
15 and appropriate measures to be implemented by manufacturers.
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18 **Falsified medicines**

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20 Only four incidents of falsified medicines were reported by Health Canada. The
21 detection is extremely low compared with substandard medicine. Health Canada has
22 robust GMP inspections that cover all drug establishments including manufacturers,
23 distributors and wholesalers. The reporting system of Health Canada is concerned
24 with falsified medicines detected within the scope of GMP inspections.¹⁸ Some
25 falsified medicines may be intercepted and seized by enforcement bodies on their
26 way to target destinations, but not necessarily intended for the Canadian market.
27 This may explain the low detection rate by Health Canada.
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30 **Comparison with the UK**

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32 Canada and the UK are two of the top pharmaceutical markets in the world, holding
33 equal global pharmaceutical market share values of USD \$21,877 and USD \$21,635
34 billion, respectively.²² They also use similar approaches in dealing with substandard
35 medicines based on the expected risk. In the UK, the drug regulator uses four
36 classes of drug alerts to communicate the risk of substandard medicines to
37 Healthcare professionals.⁶ A request to recall the affected batches is issued with the
38 first three classes (class 1-3 drug alerts), comparable to the Health Product recall
39 type I, II and III issued by Health Canada. A class 4 drug alert is issued by the UK
40 drug regulator when a drug recall is not required, but caution is needed to deal with a
41 substandard medicine. This type of communication is similar to the PA, HPC-NtoH
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3 and HPC-DHCPL used by Health Canada. A class 1 drug recall (issued in the UK),
4 and both the Health Product recall type I and PW (issued in Canada) are considered
5 to be urgent communications. The rest of the documents in both countries are
6 deemed as semi-urgent communications.^{6, 14}
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10 Out of the 280 substandard medicines found in the UK, 17 (6%) were subject to
11 urgent communication.⁷ The corresponding number in Canada was 89 (13%) out of
12 649. Overall, a larger number of substandard medicines were found in the Canadian
13 supply chain (649 medicines) than in the UK (280 medicines).⁷ The major contributor
14 to this difference in our data was the number of medicines recalled due to stability
15 problems (Figure 3), which were responsible for 50% of the difference. The
16 differences in stability issues between Canada and the UK require further
17 investigation.
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20 21 22 23 24 25 **Limitations**

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27 This study encountered some limitations. Firstly, the expected adverse events
28 associated with the use of substandard medicines were not reported by Health
29 Canada or the manufacturers. Moreover, the adverse reaction database **does not**
30 **state the batch numbers of medicines reported with the complaint. Therefore we**
31 **could not compare the expected risk associated with the recalled batches of**
32 **substandard medicines with the adverse drug reaction database.** Thus, the clinical
33 significance of the problem is unknown.
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42 43 44 45 **CONCLUSION**

46 Substandard medicines are **an increasing** problem in Canada and have resulted in a
47 large number of recalled medicines. Most of the failures were related to stability
48 issues, raising the need to investigate the root causes and for stringent preventative
49 measures to be implemented by manufacturers. Regular GMP inspections on
50 manufacturing sites were highlighted in this review as some of the most important
51 tools that can improve detection of substandard medicines.
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Contributors:

TA and IC conceived the study design and planned the research. TA performed the database search, extracted the data and drafted the manuscript. HS double-checked the extracted data, and interpreted the results. IC and HS edited and reviewed the manuscript. All authors approved the final version of the manuscript.

Competing interests: None.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Ethical approval: Not required.

Data sharing: No additional data available.

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TABLES:

Table 1: Substandard medicines

Defect Type	Number of medicines	%	Defect details	Number of medicines
Stability defects	205	32	Concern about stability of active ingredients	63
			Levels of impurities in excess of specification at different time points	50
			Dissolution, disintegration and drug release failure	45
			Others	47
Contamination	139	21	Impurities	82
			Lack of sterility assurance	35
			Microbial contamination	22
Minor packaging defects	71	11	Fault involving the external packaging or minor printing errors that do not involve name or strength of a medicines	60
			Missing or incorrect product registration number, batch number, manufacturer's name or expiry date	11
Major packaging defects	65	10	Missing or incorrect name ,strength, or active ingredient of a medicine on carton or box	35
			Packing a medicine in the wrong carton or present of a foreign tablet or capsule in the bottle or blister	30
Defects in active ingredient	62	10	Excessive amount of active ingredients	26
			Inadequate amount of active ingredient	20
			Active ingredient is out of specification	16
Delivery defects	35	5	Fault with a device	22
			Leakage or loose/ tight seal ,cracks in a vial or broken tablets	9
			Others	4
Other defects	72	11	GMP deficiencies and deviation from preapproved specifications	48
			Inappropriate shipment	14
			Dissolution / disintegration failure	10
Total	649	100		649

Table 2: Contaminated medicines subjected to urgent recalls (Health Product Recall type I).

Medications (number of incidents)	Formulation	Defect description
Marcaine (2), acyclovir (1), nitroglycerin (1), magnesium sulfate (1), dexamethasone sodium (1), vistide (1) and carboplatin (1)	Solution for injection	Visible particulates were identified in the formulation (such as white, metallic or glass particles.)
Propofol (4) and fat emulsion (1)	Emulsion for injection	
Extraneal (1) ciprofloxacin (1), carmustine (1), technetium Tc 99m (1) and liposomal amphotericin B (1)	Solution for injection	Microbial contamination (bacterial, fungal or viral contamination)
Docusate sodium (1)	Capsules	
Sucrose (1)	Oral liquid	
Benzalkonium chloride (1)	Topical Liquid	
Sodium Chloride (1) and dextrose (1)	Solution for injection	Integrity of the foil seal is compromised leading to potential contamination of the vial adapter
Diameal (1), DTE technetium Tc 99m (1), electrolyte infusion (1) and dextrose (1)	Solution for injection	Lack of sterility assurance at the time of manufacture
Gen Teal Artificial Tears (1)	Ophthalmic Solution	
Heparin sodium (3)	Solution for injection	Contamination with heparin-like contaminant
Quetiapine (3)	Tablets	cross-contamination of trace amounts of clindamycin in quetiapine active pharmaceutical ingredient during the manufacturing process

Note: All medicines were reported using health Product Recall Type I document

Table 3: Substandard medicines subjected to urgent recalls (Health Product Recall type I and PW) with other defect types

Type of defect	Medications (number of incidents)	Formulation	Defect description
Major packaging defects (incorrect labelling)	Trazodone (1), amlodipine (1) and fluvoxamine (1)	Tablets	Some products contained the wrong medicines due to labelling errors (e.g., amlodipine instead of minocycline, minocycline instead of amlodipine, clonazepam instead of rifampicin and fluphenazine instead of Octreotide) or filling errors (e.g., nabilone instead of trazodone, ciprofloxacin instead of fluvoxamine, trazodone instead of nabilone, Isoproterenol instead of morphine and blue collyrium instead of prednisolone)
	Nabilone (1), minocycline (1) and rifampicin (1)	Capsules	
	Morphine sulphate (1) and octreotide acetate omega (1)	Solution for injection	
	Prednisolone (1)*	Ophthalmic solution	
	Hemodialysis acid concentrates (1), remifentanil HCl (1), pamidronate disodium (1), tobramycin (1) and triamcinolone acetonide (1)	Solution for injection	Wrong strength , dosage or expiry date were printed on the packaging
	Sodium solysterene sulfonate (1)	Suspension	
	Acetaminophen (1)	Suppositories	
	Personnelle cold and flu tablets (2), acetylsalicylic acid (1), acetaminophen (1) and Personelle acid control (1)	Tablets	Important mandatory warning statement was missed on the external packaging
	Oral contraceptive pills (4)	Tablets	Additional placebo tablet was found in place of an active tablet in one blister pack raising the risk of unwanted pregnancy
Ibuprofen (2)	Tablets	The label stated that the bottle had a child resistant cap, but the cap used was not child resistant.	
Stability defects	Smallpox vaccine (1)	Solution for injection	Evidence of instability based on its appearance.
	Timolol (1)	Ophthalmic Solution	Active ingredient was out of specification after 12 month of production date
	Valproic acid (1)	Capsules	Disintegration test failure within the shelf life of the drug
	Amoxicillin (1)	Suspension	Out of specification assay result was obtained at various time points.
Active ingredients defects	Phenobarbital (1)* and morphine SR (1)	Tablets	Oversized tablets were found raising the risk of overdose
	Acetylsalicylic acid (1)		Inadequate amount of active ingredient
	Delflex (1) and carmustine (1)	Solution for injection	Excessive amount of active ingredients
	Ethacrynic acid (1)		Inadequate amount of active ingredient
Delivery defects	Paliperidone palmitate (1), nutrinal (1), degarelix (1), caspofungin acetate (1), vancomycin (1) and argatroban (1)	Solution for injection	Cracks in the syringes or vials , or leaks from the bags were identified raising the risk of contamination
	Sumatriptan (1)		Pre-filled syringes were filled with needles that protruded through the needle shield
	Morphine sulphate (1)		Plunger friction with the vial may cause pump occlusion or delivery of inaccurate dose
	Cough and Cold syrup (9)	Syrup	The child-resistant feature of the bottle cap was not functioning properly
Other	Hypromellose (1)	lubricant eye gel	Non-compliance with Good manufacturing practices

*Medicine was reported using the Public Warning document. Others were reported using Health Product Recall type I

Table 4: Substandard medicines categorised by the type of the Marketing Authorisation Holders

Type of quality defect	Medicines marketed by manufacturers (n= 122)	Medicines marketed by distributors (n= 26)	P-Value*
	Number of medicines, (%)	Number of medicines, (%)	
Stability	191 (31)	14 (37)	0.476
Contamination	134 (22)	5 (13)	0.228
Minor packaging	69 (11)	2 (5)	0.417
Major packaging	60 (10)	5 (13)	0.573
Active ingredient	59 (10)	3 (8)	1.000
Delivery	34 (5)	1 (3)	0.714
Others	64 (11)	8 (21)	0.058
Total	611 (100)	38 (100)	

*A significant difference was defined at a p value <0.05.

Figure legends:

Figure 1: Flow diagram of search and resulting incidents.

Figure 2: Number of incidents of defective medicines reported by Health Canada.

Figure 3: Comparison between Canada and the UK in the types of substandard medicines.

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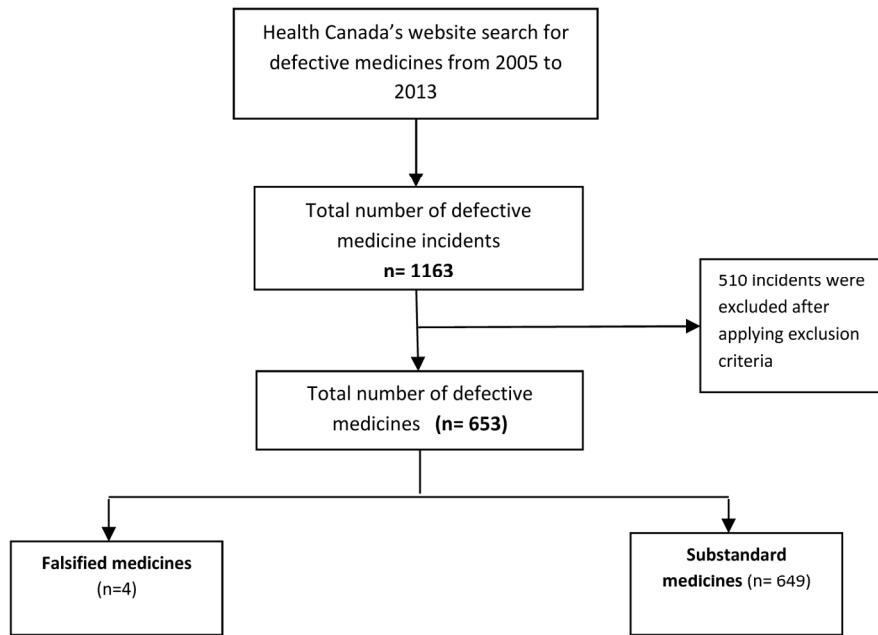


Figure 1: Flow diagram of search and resulting incidents.
148x103mm (300 x 300 DPI)

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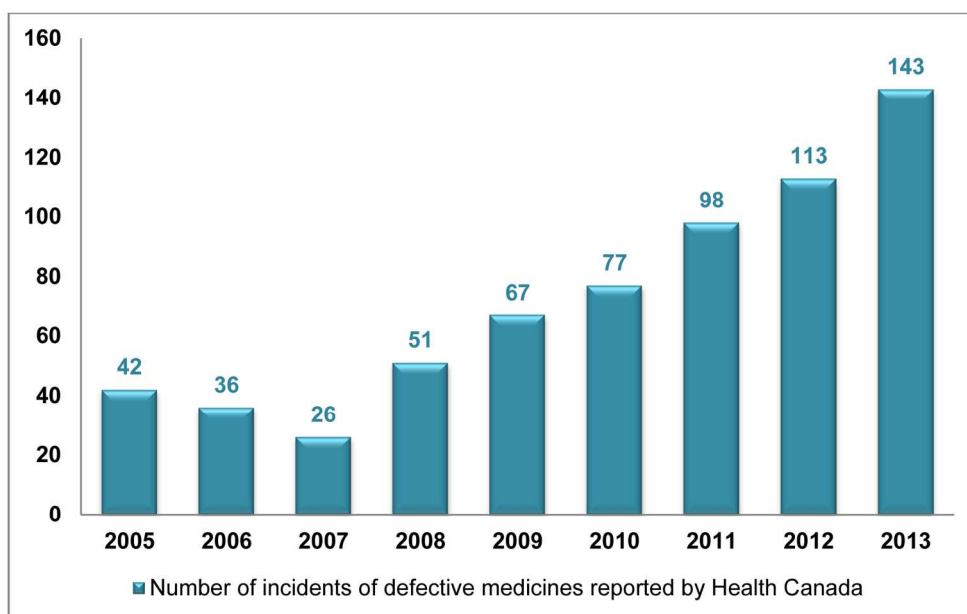


Figure 2: Number of incidents of defective medicines reported by Health Canada.
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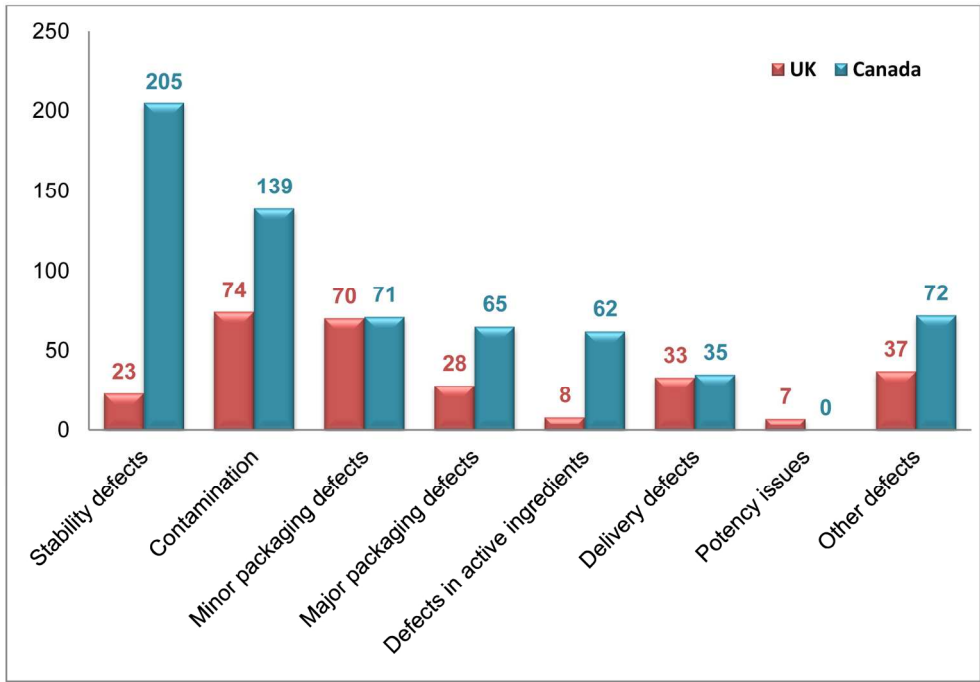


Figure 3: Comparison between Canada and the UK in the types of substandard medicines. 157x109mm (300 x 300 DPI)

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Supplementary data:**Table 1: Number of formulations under each defect type of substandard medicines**

Defect Type	Formulation type	Number of formulations
Stability defect	Tablets	89
	Parenteral	46
	Topical preparations	34
	Capsules	24
	Liquid preparations	12
Contamination	Parenteral	71
	Tablets	29
	Topical preparations	21
	Liquid preparations	11
	Capsules	7
Minor packaging defect	Tablets	39
	Parenteral	14
	Capsules	9
	Liquid preparations	5
	Topical preparations	4
Major packaging defects	Tablets	35
	Parenteral	13
	Capsules	11
	Topical preparations	6
Defect in active ingredient	Tablets	18
	Topical preparations	16
	Parenteral	13
	Liquid preparations	8
	Capsules	6
Delivery defect	Parenteral	11
	Liquid preparations	10
	Topical preparations	8
	Tablets	6
	Capsules	1
Other defects	Tablets	35
	Parenteral	20
	Topical preparations	11
	Liquid preparations	3
	Capsules	3
Total		649

**Table 2: Substandard medicines subjected to semi-urgent communications
(Health Product Recall - Types II and II, PA, HPC-NtoH and HPC-DHCPL)**

Type of defect	Health Product Recalls - type II	Health Product Recalls - type II	PA	HPC-NtoH	HPC-DHCPL	Type of drug recall was not stated
Stability defects	90	107	0	0	1	0
Contamination	68	25	1	6	2	0
Minor packaging defects	22	47	0	2	0	0
Defects in active ingredient	33	22	0	0	1	1
Major packaging defects	23	12	1	1	0	1
Delivery defects	10	6	5	0	2	0
Other issues	42	26	1	0	1	1
Total	288	245	8	9	7	3

PA: Public Advisory; **HPC-DHCPL:** Healthcare Professional Communication - Dear Health Care Professional Letter; **HPC-NtoH:** Healthcare Professional Communication - Notice to Hospitals

Table 3: Substandard medicines reported by Health Canada, classified according to the organ or system in which they act and according to the therapeutic subgroup they belong (Classification ATC) 2005-2013:

Category	No.	%	Category	No.	%
According to organ or system in which the drug acts			According to subgroup, therapeutic main group		
Nervous system	141	21.7	Analgesics Psycholeptics Psychoanaleptics Anaesthetics Antiepileptics Anti-parkinson drugs	65 26 18 15 13 4	10.0 4.0 2.8 2.3 2.0 0.6
Alimentary tract and metabolism	90	13.9	Drugs for acid related disorders Vitamins Mineral supplements Laxatives Drugs used in diabetes Drugs for constipation Stomatological preparations	25 22 16 12 9 3 3	3.9 3.4 2.5 1.8 1.4 0.5 0.5
Cardiovascular System	83	12.8	Antihypertensives Lipid modifying agents Cardiac therapy	50 24 9	7.7 3.7 1.4
Anti-infectives for systemic use	65	10.0	Antibacterials for systemic use Antimycotics for systemic use Immune sera and immunoglobulins Vaccines Antivirals for systemic use	38 8 8 6 5	5.9 1.2 1.2 0.9 0.8
Blood and blood forming organs	63	9.7	Blood substitutes and perfusion solutions Antithrombotic agents Antianemic preparations	30 19 14	4.6 2.9 2.2
Dermatologicals	46	7.1	Corticosteroids, dermatological preparations Other dermatological preparations Anti-acne preparations Antifungals for dermatological use	18 14 9 5	2.8 2.2 1.4 0.8
Respiratory system	31	4.8	Antihistamines for systemic use Cough and cold preparations Drugs for obstructive airway diseases Nasal preparations	11 11 7 2	1.7 1.7 1.1 0.3
Genito-urinary system and sex hormones	29	4.5	Sex hormones and modulators of the genital system Urologicals Gynecological antiinfectives and antiseptics	22 5 2	3.4 0.8 0.3
Antineoplastic and immunomodulating agents	28	4.3	Antineoplastic agents Immunosuppressants Immunostimulants Endocrine therapy	18 4 4 2	2.8 0.6 0.6 0.3
Various	26	4.0	Diagnostic radiopharmaceuticals All other therapeutic products Contrast media	20 4 2	3.1 0.6 0.3
Sensory organs	21	3.2	Ophthalmologicals Otologicals	20 1	3.1 0.2
Musculo-skeletal system	18	2.8	Antiinflammatory and antirheumatic products Drugs for treatment of bone diseases Muscle relaxants	11 6 1	1.7 0.9 0.2
Systemic hormonal preparations, excluding sex hormones and insulins	8	1.2	Pituitary and hypothalamic hormones and analogues Pancreatic hormones Pituitary and hypothalamic hormones and analogues	3 3 2	0.5 0.5 0.3
Total	649	100	Total	649	100

Table 4: Substandard medicines categorised by manufacturers and type of defects

Manufacturer*	Number of medicines under each type of quality defect							Total	Total number of medicines marketed by each manufacturer in Canada
	Stability	Contamination	Minor packaging	Active ingredient	Major packaging	Delivery	Others		
Apotex Inc.	31	13	4	2	2	2	3	57	220
Teva Canada Ltd.	15	11	5	7	10	2	3	53	224
Pharmascience Inc.	12	3	3	6	6	2	3	35	173
Vita Health Products Inc.	4	0	14	4	10	1	0	33	NA
Sandoz Canada Inc.	5	8	1	12	5	0	0	31	232
Hospira Healthcare Co.	1	13	0	0	0	3	9	26	94
Novartis Pharmaceuticals Canada Inc.	4	2	1	1	1	13	1	23	114
Pfizer Canada Inc.	10	2	4	1	1	1	1	20	120
GlaxoSmithKline Inc.	3	8	2	6	0	1	0	20	77
Baxter Co.	2	8	4	0	1	1	0	16	58
Sanofi-Aventis Canada Inc.	4	1	2	5	0	0	4	16	76
Laboratoire Riva Inc	11	1	0	0	0	0	1	13	NA
Pro-Doc Ltd.	5	3	0	0	1	0	3	12	158
Mylan pharmaceuticals	0	0	2	1	4	1	3	11	145
Pharmetics Inc.	1	3	0	0	0	0	2	10	NA
JAMP Pharma Co.	4	1	1	3	0	0	1	10	37
Pharmaceutical Partners of Canada.	2	3	0	0	1	1	2	9	40
Schering-Plough Canada Inc.	3	1	2	0	0	0	2	8	72
McNeil Consumer Products Co.	0	2	1	0	0	0	5	8	28
Taro Pharmaceuticals Inc.	3	3	0	0	0	0	1	7	21
								418	

*Only the top 20 manufacturers are listed.

BMJ Open

Quality of medicines in Canada: a retrospective review of risk communication documents (2005–2013)

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-006088.R2
Article Type:	Research
Date Submitted by the Author:	06-Oct-2014
Complete List of Authors:	Almuzaini, Tariq; University of Nottingham, Academic Division of Child Health Sammons, Helen; University of Nottingham, Child Health Choonara, Imti; University of Nottingham, Academic Division of Child Health
Primary Subject Heading:	Public health
Secondary Subject Heading:	Health policy, Pharmacology and therapeutics
Keywords:	Substandard medicines, Falsified medicines, Drug recalls

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3 **Quality of medicines in Canada: a retrospective review of risk**
4 **communication documents (2005–2013)**
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38
39 **Abstract:** 252 words
40

41 **Full text:** 3589 words
42

43 **Number of figures:** 3
44

45 **Number of tables:** 4
46
47

48
49 **Keywords:** Falsified, substandard, defective, medicines, recalls
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ABSTRACT

Objective: To explore the quality and safety of medicines in Canada.

Design: A retrospective review of drug recalls and risk communication documents conveying issues relating to defective (i.e., substandard and falsified) medicines.

Setting: The Health Canada website search for drug recalls and risk communication documents issued between 2005 and 2013.

Eligibility criteria: Drug recalls and risk communication documents related to quality defect in medicinal products.

Main outcome measure: Relevant data about defective medicines reported in drug recalls and risk communication documents, including description of the defect, type of formulation, year of the recall and category of the recall or the document.

Results: There were 653 defective medicines of which 649 were substandard. The number of defective medicines reported by Health Canada increased from 42 in 2005 to 143 in 2013. The two most frequently reported types of defects were stability (205 incidents) and contamination issues (139 incidents). Some of these defects were found to be more prominent and repetitive over other types within some manufacturers. Tablet formulation (251 incidents) was the formulation most frequently compromised. No significant differences were observed between the manufacturers and distributors in the number of substandard medicines reported under each defect type. There were only four falsified medicines reported over the nine-year period.

Conclusions: Substandard medicines are a problem in Canada and have resulted in an increasing number of recalled medicines. Most of the failures were related to stability issues, raising the need to investigate the root causes and for stringent preventative measures to be implemented by manufacturers.

Strengths and limitations of this study

- It is the first review to assess the problem of defective medicines in Canada.
- It quantifies and analyses drug recalls in Canada over a 9- year period.
- Clinical significance of the problem is undetermined, owing to the lack of data from Health Canada regarding adverse events associated with the use of defective medicines.

INTRODUCTION

Defective medicines are a major public health problem¹⁻⁴ Different surveys in lower income countries (LIC) and lower-middle-income countries (LMIC) have found that defective medicines are readily available.^{3, 5}

Defective medicine is a term used to describe any drug with a quality defect, whether the error was due to deliberate falsification or unintentional error during manufacturing.^{6, 7} It is a large category that comprises two main types of compromised drugs, substandard and falsified medicines. A substandard medicine is a medicine that does not meet the regulator standards due to an unintentional or negligent error.⁸ A falsified medicine, however, is one where deliberate and criminal intent is involved.⁸

In high income countries (HIC), there have been no studies with good methodological quality examining the overall prevalence of substandard or falsified medicines.³ The surveillance system in HIC in Europe and North America, however, is a well-established system that has identified and withdrawn several medicines from the market with serious safety concerns.^{9, 10} These surveillance systems have reported numerous incidents of substandard and falsified medicines, and highlighted the problem of such drugs in these countries. Examples of these are the falsified cancer drug, Avastin, and substandard spinal steroid injections reported in the USA.^{11, 12} In our previous study on the UK, we studied the problem of defective medicines in the UK by reviewing the drug alerts issued by the drug regulator over an 11-year period. The study showed that substandard medicines are a problem that appears to be increasing.⁷ We wished to explore another HIC and chose Canada, as the problem of

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3 defective medicines has never been explored in this setting and because of the level of
4 data available in the public domain.
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7 In Canada, Health products are regulated by Health Canada, which is the federal
8 department responsible for the monitoring and regulating of medicines.¹³ It issues a
9 number of risk communication documents to the public and healthcare professionals.
10 These involve identification of the possible risk, assessment of its severity and
11 clarification of the nature of the problem. This communication is also initiated to
12 disseminate information regarding new safety issues of medicines or existing health
13 risks to allow healthcare professionals and their patients to make well-informed
14 decisions about their health.¹⁴
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21 The aim of this study was to explore the quality and safety of medicines in Canada by
22 analysing the risk communication documents conveying issues relating to defective
23 medicines.
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29 **METHODS**

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31 Health Canada uses 13 risk communication documents, which can be issued for the
32 public, healthcare professionals, and hospitals.¹⁴ A preliminary search for these risk
33 communication documents found that only five documents can be used by Health
34 Canada to convey any defective health product issue in the Canadian official supply
35 chain. These can be described as follows:
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- 40 • **Public Warning (PW):** issued by Health Canada if the use of the drug can
41 cause a severe adverse health consequence that may lead to death.
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- 43 • **Public Advisory (PA):** issued by Health Canada if exposure to or the use of
44 the drug can cause adverse health consequences, but is not life threatening
45 or serious.
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- 47 • **Healthcare Professional Communication - Notice to Hospitals (HPC-
48 NtoH):** to inform the healthcare professional about time-sensitive issues
49 concerning safety and/or efficacy of medicinal products. It is intended for
50 hospital use only.
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- **Healthcare Professional Communication - Dear Health Care Professional Letter (HPC-DHCPL):** to inform the healthcare professional about issues regarding safety and/or efficacy of medicinal products.
- **Health Product Recall (with type I, II or III):** These can be classified according to the urgency of the recall as follows:
 - Health Product Recall type I: issued if the health product can cause severe adverse health consequence that may lead to death.
 - Health Product Recall type II: issued if the exposure to or the use of the health product can cause adverse health consequences but is not life threatening or serious.
 - Health Product Recall type III: The exposure to or use of the health product is not likely to cause any harm but the recall is initiated for other reasons such as minor deviation from specifications.

Both PW and Health Product Recall type I are considered by Health Canada to be urgent communications, as they are issued for a medicine which may pose a serious health risk. PA, HPC-NtoH, HPC-DHCPL and type II and III Health Product Recalls are semi-urgent communications where the risk associated with the use of a medicine is not serious.¹⁴

A search for risk communication documents conveying issues relating to defective medicines (i.e., substandard and falsified medicines) was carried out. This was performed through the official Health Canada's website and using the search engine allocated for advisories, warnings, and recalls of health products (<http://www.hc-sc.gc.ca/dhp-mpps/medeff/advisories-avis/index-eng.php>). Health Canada started posting Health Product Recalls on its website in 2005. These recalls are the main tool that Health Canada uses to convey quality issues with medicines. Before that, there were only two types of risk communication documents (PA and HPC-DHCPL) available on Health Canada's website. We wanted to examine the same documents throughout the years. Therefore, the search was started from 2005, and all risk communication documents issued between 1 January 2005 and 31 December 2013 were included. All risk communication documents (PW, PA, HPC-DHCPL, HPC-NtoH and Health Product Recalls) were reviewed and the relevant information was then extracted.

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3 All relevant information regarding defective health products was compiled and
4 exclusion criteria were as follows: veterinary medicines; medicines lacking efficacy or
5 acquiring general safety issues; herbal and probiotic products; dietary and cosmetic
6 products; and other natural health product recalled for regulatory reason (i.e., those
7 do not have a valid marketing authorisation). The following data were extracted from
8 the risk communication documents: name, strength, and dosage form; year of the
9 document; nature of the defect; type of drug recall (in the case of Health Product
10 Recalls); and action to be taken by healthcare professionals or the public regarding
11 the defective medicine. In the case of Health Product Recalls and PW, the action is
12 to remove the defective medicine from the dispensary shelves and contact the
13 manufacturer for return. Whereas, with other risk communication documents where
14 there is no recall required, healthcare professionals and the public are given advice
15 on how to deal with defective medicines and to alert the public to be aware of
16 expected risks. Two types of drugs can be distinguished from risk communication
17 documents; substandard drugs and falsified drugs. The decision on which incident
18 was falsified or substandard is that published by Health Canada.
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30 The type of defects were then classified using the same classification as used in our
31 previous study.⁷ The quality defects were classified as contamination, minor or major
32 packaging defect, delivery (e.g., leaking bags) defect, stability failure, potency
33 issues, active ingredient defect and other issues (such as other deviations
34 concerning non-compliance with good manufacturing practice at manufacturing site).
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39 The WHO Organization Anatomical Therapeutic Chemical (ATC) Classification
40 System was used to classify defective medicines.¹⁵ The first level of this classification
41 categorises medicines according to the organ or system in which they act and the
42 second level classifies medicines according to their main therapeutic group. This
43 was performed to highlight the most frequent therapeutic classes affected by these
44 recalls.
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50 **Method of analysis**

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52 Minitab (version 16) software was used to store and analyse the data. Descriptive
53 statistics were used to summarise the results. Marketing authorisation holders of
54 recalled medicines were either licensed manufacturers or distributors. A comparison
55 between the manufacturers and distributors in the number of substandard medicines
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3 reported under each type of quality defect was carried out using Fisher's exact test.
4 A significant difference was defined at a p value <0.05. The comparison was
5 conducted to investigate if there are certain types of quality defects (e.g., stability or
6 packaging issues) that were more likely to be reported with distributors, as this may
7 indicate non-compliance with Good Distribution Practices.
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11 **RESULTS**

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13 A total of 653 defective medicines were identified in the Canadian supply chain
14 (Figure 1). Among these defective medicines, 649 were found to be substandard
15 medicines, and only four were found to be falsified medicines in the nine years
16 studied. The rate of reporting defective medicines has increased each year over the
17 last six years (Figure 2).
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23 **Substandard medicines**

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25 Substandard medicines represent the bulk of defective medicines ($n= 649$, 99%)
26 reported by Health Canada. The two most frequent types of defects reported were
27 stability ($n= 205$, 32%) and contamination ($n= 139$, 21%) issues (Table 1). It is clear
28 that substandard medicines with stability defects represent the largest group. The
29 majority of these formulations were found to have degraded one year after their
30 release into the market, resulting in low concentrations of active ingredients,
31 impurities, dissolution and disintegration failures. Tablets were the formulation most
32 frequently reported to be substandard (supplementary table 1).
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40 Among the 649 substandard medicines, 89 (14%) were subjected to urgent
41 communications and therefore required urgent recalls. These medicines were
42 reported using the Health Product Recall type 1 ($n= 87$) and the PW ($n=2$). More
43 than half of these medicines ($n= 46$, 53%) were parenteral formulations (Tables 2
44 and 3). Of the 89 medicines that were recalled, 34 were contaminated. The majority
45 of these were parenteral formulations that were recalled due to the presence of
46 particulate matters, the presence of microbes, or a lack of sterility assurance during
47 their manufacture (Table 2). The remaining substandard medicines ($n= 55$) were
48 urgently recalled due to other types of defects (Table 3), mainly packaging defects or
49 delivery issues (such as cracks in the vials or leaks in the bags, as well as faults in
50 the unit used to deliver the medicines). Packaging defects were one of the major
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3 clinical issues reported, and these included incorrect labelling (i.e., wrong drug
4 name, strength, or expiry date) and packaging that lacked important information
5 regarding safety or the use of medicines in the patient information leaflets. In some
6 cases, the labelling was correct, but the wrong medicines were filled, resulting in
7 major and urgent recalls of affected batches (Table 3).
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12 Other substandard medicines ($n= 560$, 86%) were subjected to semi-urgent recalls
13 ($n= 536$) or caution in use ($n= 24$). These were reported via the Health Product
14 Recall type II ($n= 288$ medicines, 44%) and III ($n= 245$, 38%), PA ($n= 8$, 1%), HPC-
15 NtoH ($n= 9$, 1%) and HPC-DHCPL ($n= 7$, 1%). Three medicines were recalled, but
16 the corresponding type of Health Product Recall was not given by Health Canada.
17 The majority of these drugs had stability, contamination and packaging defects
18 (supplementary table 2).
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Drugs that act on the nervous system ($n= 141$, 22%), alimentary tract and
metabolism ($n= 90$, 14%), and cardiovascular system ($n= 83$, 13%) were the
subgroups that most frequently contained substandard medicines. When the second
level of this classification (i.e., therapeutic classification) was used, the top three
groups reported to be substandard were analgesics ($n= 65$, 10%), antihypertensives
($n= 50$, 8%) and antibacterials ($n= 38$, 6%) (supplementary table 3).

Substandard medicines categorised by manufacturers

The review identified 122 licensed manufacturers and 26 licensed distributors. Manufacturers held the marketing authorisation for 611 substandard medicines and distributors for 38 (Table 4). No unlicensed manufacturers or distributors were involved. A comparison between those manufacturers and distributors in the number of substandard medicines reported under each defect type and the p values for these differences is presented in Table 4. No significant differences were observed between manufacturers and distributors.

The top 20 manufacturers are listed in supplementary table 4. It was noted that 50% or more of substandard medicines manufactured by Apotex Inc., Pfizer Canada Inc. and Laboratoire Riva Inc. had stability issues. Almost half of the substandard products from Baxter Co., Hospira Healthcare Co. and GlaxoSmithKline Inc. were

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3 contaminated. Products of Sandoz Canada Inc. had a problem with the active
4 ingredient; the concentration was either too high or too low. More than half of
5 Novartis products, which are reported to be substandard, were recalled due to
6 delivery concerns, such as failure of the child-resistant feature of the bottle cap or
7 leaks in the infusion bags.
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11 12 13 14 **Falsified medicines** 15

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17 Four incidents of falsified medicines were identified in Canada's supply chain
18 between 2011 and 2013. All these incidents involved two sexual enhancement
19 medicines, Viagra® (sildenafil) and Cialis® (tadalafil).
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23 In all cases of falsified medicines, Public Advisories were issued to inform the public
24 to contact their healthcare professionals if they had concerns about these falsified
25 medicines. The public was also advised to verify that these products were assessed
26 by Health Canada for safety by looking at the authorisation number printed on the
27 label. These medicines were seized in the retail outlets in Canada, and no further
28 information was given by Health Canada about the subsequent investigation or
29 action taken by Health Canada.
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38 **DISCUSSION** 39

40 This is the first review that discusses the issue of substandard and falsified
41 medicines in Canada by evaluating the risk communication documents and drug
42 recalls posted on Health Canada website. Our observations of defective medicines
43 recalls over nine consecutive years, from 2005 to 2013, have shown that the recall of
44 substandard medicines is an increasing trend. It is concerning that over half of the
45 stability failures were related to instability of active ingredients or dissolution and
46 disintegration failure. Both defects have the potential to affect the bioavailability of
47 the active ingredients in the systemic circulation, and in turn, may lead to therapeutic
48 failure.
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Substandard medicines

The most frequent type of formulation reported to be substandard were tablets. Tablets have a slow onset of action and require less precaution in terms of sterility, than parenteral formulations. The extent of adverse consequences that can arise from failure to comply with manufacturing requirements, however, cannot be ignored. This was evident from the death of 120 patients in Pakistan due to contamination of isosorbide mononitrate tablets with large doses of an antimalarial drug.¹⁶ Another of the most pronounced examples is the phenobarbital and morphine tablet recalls in Canada. Oversized tablets (i.e. tablets that exceed the weight requirement) were found in both drugs, raising the risk of the patients taking as much as double the strength stated on the bottle (Table 3). The Institute for Safe Medication Practices (ISMP), a non-profit organisation, stated that the US manufacturer (KV Pharmaceutical) received abnormally high reports of serious adverse events concerning overdose of these recalled tablets.¹⁷ However, owing to the lack of sufficient details, it was impossible to link the overdose events specifically to the substandard tablets. The Adverse events relating to this defect have not been documented by Health Canada.

It was uncertain whether the rise of substandard medicines incidents were related to improved detection by Health Canada or due to an increase of substandard medicine production by manufacturers. The rate of increased incidence of substandard medicines could be associated with the implementation of improved detection policies and regulations by Health Canada. Introduction of Good Manufacturing Practices (GMP) inspection policy for Canadian drug establishments may be one of the explanations.¹⁸ Since 1996, there have been numerous changes in GMP guidelines and international agreements. These led Health Canada to update its policy on GMP inspection in January 2008 as a response to harmonise its GMP compliance programme with drug regulatory authorities in other countries.¹⁸ Subsequently, there has been a steady increase of incidents of substandard medicines from 2008 to 2013 (Figure 2). Similarly, it has been highlighted that most of the FDA recalls were related to FDA inspectors' visits in the USA.¹⁹

The GMP policy illustrates the procedures Health Canada follows to ensure that all drug establishments comply with GMP guidelines. This is conducted via inspections

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3 with varying cycles according to a risk-based approach to assess complaints about
4 medicines, and a ranking scale of priority.¹⁸This assessment is to ensure that these
5 complaints are dealt with in a timely manner. The performance of Health Canada in
6 using the risk-based approach, however, was criticised in the 2011 report of the Auditor
7 General of Canada.²⁰ Based on a representative sample (50) of the files that Health
8 Canada received in 2009 and 2010 concerning drug-related complaints, only 27 were
9 dealt with according to the established risk-based standard operating procedures for
10 prioritising reported complaints. The report concluded that Health Canada did not
11 consistently apply its risk-based approach and therefore some of these complaints
12 might not be processed in a timely manner proportional to their expected risk.²⁰
13 Therefore, the possibility that the increase in substandard medicines was a result of
14 poor manufacturing practices cannot be excluded.
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24 **Manufacturing errors and investigation of the root cause**

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26 It is the responsibility of the manufacturers and marketing authorisation holders to recall
27 their substandard products after consultation with Health Canada. The majority of these
28 recalls were issued by the manufacturers or marketing authorisation holders using the
29 Health Product Recall type I, II and III, which accounted for 95% of the total
30 substandard medicines reported. Stability issues were mainly identified by the
31 manufacturers during on-going stability testing. However, it is unknown whether these
32 defects were identified by internal auditing systems of the manufacturers, by
33 intervention of the Health Canada inspection team or by reports from healthcare
34 professionals.
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42 Analysing pharmaceutical product recalls can be of great importance to identify the root
43 causes of recalled medicines. The prompting of a drug recall can be regarded as a
44 disastrous failure of the manufacturer's quality plan. Even with stringent quality
45 measures, errors can occur.^{21, 22} Thus, it is very important to identify the root cause of
46 the defects to avoid similar episodes in the future. The root cause for a defect is
47 required to be submitted to Health Canada, as soon as it is identified, along with other
48 information relating to the quantity and depth of the distribution of the affected
49 medicine. It is the responsibility of Health Canada to monitor the overall procedure and
50 assess the root cause for this problem and, if required, to conduct an inspection to
51 verify that a corrective action is implemented.^{23, 24} It has been highlighted in this review
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3 that stability failure and contamination issues were the defect types being reported
4 most frequently. These issues affected several manufacturers on more than one
5 occasion (supplementary table 4). This highlights the need for root cause investigations
6 and appropriate measures to be implemented by manufacturers as well as effective
7 monitoring by Health Canada.
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10 11 **Falsified medicines**

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14 Only four incidents of falsified medicines were reported by Health Canada. The
15 detection is extremely low compared with substandard medicine. Health Canada has
16 robust GMP inspections that cover all drug establishments including manufacturers,
17 distributors and wholesalers. The reporting system of Health Canada is concerned
18 with falsified medicines detected within the scope of GMP inspections.¹⁸ Some
19 falsified medicines may be intercepted and seized by enforcement bodies on their
20 way to target destinations, but not necessarily intended for the Canadian market.
21 This may explain the low detection rate by Health Canada.
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28 29 **Comparison with the UK**

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31 Despite the fact that Canada and the UK represent 2% (for each) of the global
32 pharmaceutical market volume, they are two of the top markets by value of marketed
33 medicines. Canada and the UK hold equal global pharmaceutical market share
34 values of USD \$21,877 and USD \$21,635 billion, respectively.²⁵ They also use
35 similar approaches in dealing with substandard medicines based on the expected
36 risk. In the UK, the drug regulator uses four classes of drug alerts to communicate
37 the risk of substandard medicines to Healthcare professionals.⁶ A request to recall
38 the affected batches is issued with the first three classes (class 1-3 drug alerts),
39 comparable to the Health Product recall type I, II and III issued by Health Canada. A
40 class 4 drug alert is issued by the UK drug regulator when a drug recall is not
41 required, but caution is needed to deal with a substandard medicine. This type of
42 communication is similar to the PA, HPC-NtoH and HPC-DHCPL used by Health
43 Canada. A class 1 drug recall (issued in the UK), and both the Health Product recall
44 type I and PW (issued in Canada) are considered to be urgent communications. The
45 rest of the documents in both countries are deemed as semi-urgent
46 communications.^{6, 14}
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3 Out of the 280 substandard medicines found in the UK, 17 (6%) were subject to
4 urgent communication.⁷ The corresponding number in Canada was 89 (14%) out of
5 649. Overall, a larger number of substandard medicines were found in the Canadian
6 supply chain (649 medicines) than in the UK (280 medicines).⁷ It is also important to
7 mention that the UK study was conducted over a longer period (i.e., 11 years) than
8 the one on Canada (i.e., 9 years). Therefore, the difference in the number of
9 substandard medicines may be even larger than it appears. The major contributor to
10 this difference in our data was the number of medicines recalled due to stability
11 problems (Figure 3), which were responsible for 50% of the difference. The
12 differences in stability issues between Canada and the UK require further
13 investigation.
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21 22 **Limitations**

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24 This study encountered some limitations. The expected adverse events associated
25 with the use of substandard medicines were not reported by Health Canada or the
26 manufacturers. Moreover, the adverse reaction database does not state the batch
27 numbers of medicines reported with the complaint. Therefore we could not compare
28 the expected risk associated with the recalled batches of substandard medicines
29 with the adverse drug reaction database. Thus, the clinical significance of the
30 problem is unknown.
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40 41 **CONCLUSION**

42 Substandard medicines are a problem in Canada and have resulted in an increasing
43 number of recalled medicines. Most of the failures were related to stability issues,
44 raising the need to investigate the root causes and for stringent preventative
45 measures to be implemented by manufacturers. Regular GMP inspections on
46 manufacturing sites were highlighted in this review as some of the most important
47 tools that can improve detection of substandard medicines.
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52 53 **Contributors:**

54 TA and IC conceived the study design and planned the research. TA performed the
55 database search, extracted the data and drafted the manuscript. HS double-checked
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3 the extracted data, and interpreted the results. IC and HS edited and reviewed the
4 manuscript. All authors approved the final version of the manuscript.
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8 **Competing interests:** None.
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11 **Funding:** This research received no specific grant from any funding agency in the
12 public, commercial or not-for-profit sectors.
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16 **Ethical approval:** Not required.
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20 **Data sharing:** No additional data available.
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TABLES:

Table 1: Substandard medicines

Defect Type	Number of medicines	%	Defect details	Number of medicines
Stability defects	205	32	Concern about stability of active ingredients	63
			Levels of impurities in excess of specification at different time points	50
			Dissolution, disintegration and drug release failure	45
			Others	47
Contamination	139	21	Impurities	82
			Lack of sterility assurance	35
			Microbial contamination	22
Minor packaging defects	71	11	Fault involving the external packaging or minor printing errors that do not involve name or strength of a medicines	60
			Missing or incorrect product registration number, batch number, manufacturer's name or expiry date	11
Major packaging defects	65	10	Missing or incorrect name ,strength, or active ingredient of a medicine on carton or box	35
			Packing a medicine in the wrong carton or present of a foreign tablet or capsule in the bottle or blister	30
Defects in active ingredient	62	10	Excessive amount of active ingredients	26
			Inadequate amount of active ingredient	20
			Active ingredient is out of specification	16
Delivery defects	35	5	Fault with a device	22
			Leakage or loose/ tight seal ,cracks in a vial or broken tablets	9
			Others	4
Other defects	72	11	GMP deficiencies and deviation from preapproved specifications	48
			Inappropriate shipment	14
			Dissolution / disintegration failure	10
Total	649	100		649

Table 2: Contaminated medicines subjected to urgent recalls (Health Product Recall type I).

Medications (number of incidents)	Formulation	Defect description
Marcaine (2), acyclovir (1), nitroglycerin (1), magnesium sulfate (1), dexamethasone sodium (1), vistide (1) and carboplatin (1)	Solution for injection	Visible particulates were identified in the formulation (such as white, metallic or glass particles.)
Propofol (4) and fat emulsion (1)	Emulsion for injection	
Extraneal (1) ciprofloxacin (1), carmustine (1), technetium Tc 99m (1) and liposomal amphotericin B (1)	Solution for injection	Microbial contamination (bacterial, fungal or viral contamination)
Docusate sodium (1)	Capsules	
Sucrose (1)	Oral liquid	
Benzalkonium chloride (1)	Topical Liquid	
Sodium Chloride (1) and dextrose (1)	Solution for injection	Integrity of the foil seal is compromised leading to potential contamination of the vial adapter
Diameal (1), DTE technetium Tc 99m (1), electrolyte infusion (1) and dextrose (1)	Solution for injection	Lack of sterility assurance at the time of manufacture
Gen Teal Artificial Tears (1)	Ophthalmic Solution	
Heparin sodium (3)	Solution for injection	Contamination with heparin-like contaminant
Quetiapine (3)	Tablets	cross-contamination of trace amounts of clindamycin in quetiapine active pharmaceutical ingredient during the manufacturing process

Note: All medicines were reported using health Product Recall Type I document

Table 3: Substandard medicines subjected to urgent recalls (Health Product Recall type I and PW) with other defect types

Type of defect	Medications (number of incidents)	Formulation	Defect description
Major packaging defects (incorrect labelling)	Trazodone (1), amlodipine (1) and fluvoxamine (1)	Tablets	Some products contained the wrong medicines due to labelling errors (e.g., amlodipine instead of minocycline, minocycline instead of amlodipine, clonazepam instead of rifampicin and fluphenazine instead of Octreotide) or filling errors (e.g., nabilone instead of trazodone, ciprofloxacin instead of fluvoxamine, trazodone instead of nabilone, Isoproterenol instead of morphine and blue collyrium instead of prednisolone)
	Nabilone (1), minocycline (1) and rifampicin (1)	Capsules	
	Morphine sulphate (1) and octreotide acetate omega (1)	Solution for injection	
	Prednisolone (1)*	Ophthalmic solution	
	Hemodialysis acid concentrates (1), remifentanil HCl (1), pamidronate disodium (1), tobramycin (1) and triamcinolone acetonide (1)	Solution for injection	Wrong strength , dosage or expiry date were printed on the packaging
	Sodium solysterene sulfonate (1)	Suspension	
	Acetaminophen (1)	Suppositories	
	Personnelle cold and flu tablets (2), acetylsalicylic acid (1), acetaminophen (1) and Personelle acid control (1)	Tablets	Important mandatory warning statement was missed on the external packaging
	Oral contraceptive pills (4)	Tablets	Additional placebo tablet was found in place of an active tablet in one blister pack raising the risk of unwanted pregnancy
Ibuprofen (2)	Tablets	The label stated that the bottle had a child resistant cap, but the cap used was not child resistant.	
Stability defects	Smallpox vaccine (1)	Solution for injection	Evidence of instability based on its appearance.
	Timolol (1)	Ophthalmic Solution	Active ingredient was out of specification after 12 month of production date
	Valproic acid (1)	Capsules	Disintegration test failure within the shelf life of the drug
	Amoxicillin (1)	Suspension	Out of specification assay result was obtained at various time points.
Active ingredients defects	Phenobarbital (1)* and morphine SR (1)	Tablets	Oversized tablets were found raising the risk of overdose
	Acetylsalicylic acid (1)		Inadequate amount of active ingredient
	Delflex (1)and carmustine (1)	Solution for injection	Excessive amount of active ingredients
	Ethacrynic acid (1)		Inadequate amount of active ingredient
Delivery defects	Paliperidone palmitate (1), nutrinal (1), degarelix (1), caspofungin acetate (1), vancomycin (1) and argatroban (1)	Solution for injection	Cracks in the syringes or vials , or leaks from the bags were identified raising the risk of contamination
	Sumatriptan (1)		Pre-filled syringes were filled with needles that protruded through the needle shield
	Morphine sulphate (1)		Plunger friction with the vial may cause pump occlusion or delivery of inaccurate dose
	Cough and Cold syrup (9)	Syrup	The child-resistant feature of the bottle cap was not functioning properly
Other	Hypromellose (1)	lubricant eye gel	Non-compliance with Good manufacturing practices

*Medicine was reported using the Public Warning document. Others were reported using Health Product Recall type I

Table 4: Substandard medicines categorised by type of marketing authorisation holders

Type of quality defect	Medicines marketed by manufacturers (n = 122)	Medicines marketed by distributors (n = 26)	P-Value*
	Number of medicines, (%)	Number of medicines, (%)	
Stability	191 (31)	14 (37)	0.476
Contamination	134 (22)	5 (13)	0.228
Minor packaging	69 (11)	2 (5)	0.417
Major packaging	60 (10)	5 (13)	0.573
Active ingredient	59 (10)	3 (8)	1.000
Delivery	34 (5)	1 (3)	0.714
Others	64 (11)	8 (21)	0.058
Total	611 (100)	38 (100)	

*A significant difference was defined at a p value <0.05.

Figure legends:

Figure 1: Flow diagram of search and resulting incidents.

Figure 2: Number of incidents of defective medicines reported by Health Canada.

Figure 3: Comparison between Canada and the UK in the types of substandard medicines.

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3 **Quality of medicines in Canada: a retrospective review of risk**
4 **communication documents (2005–2013)**
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39 **Abstract:** 252 words
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41 **Full text:** 3589 words
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43 **Number of figures:** 3
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45 **Number of tables:** 4
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49 **Keywords:** Falsified, substandard, defective, medicines, recalls
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ABSTRACT

Objective: To explore the quality and safety of medicines in Canada.

Design: A retrospective review of drug recalls and risk communication documents conveying issues relating to defective (i.e., substandard and falsified) medicines.

Setting: The Health Canada website search for drug recalls and risk communication documents issued between 2005 and 2013.

Eligibility criteria: Drug recalls and risk communication documents related to quality defect in medicinal products.

Main outcome measure: Relevant data about defective medicines reported in drug recalls and risk communication documents, including description of the defect, type of formulation, year of the recall and category of the recall or the document.

Results: There were 653 defective medicines of which 649 were substandard. The number of defective medicines reported by Health Canada increased from 42 in 2005 to 143 in 2013. The two most frequently reported types of defects were stability (205 incidents) and contamination issues (139 incidents). Some of these defects were found to be more prominent and repetitive over other types within some manufacturers. Tablet formulation (251 incidents) was the formulation most frequently compromised. No significant differences were observed between the manufacturers and distributors in the number of substandard medicines reported under each defect type. There were only four falsified medicines reported over the nine-year period.

Conclusions: [Substandard medicines are a problem in Canada and have resulted in an increasing number of recalled medicines.](#) Most of the failures were related to stability issues, raising the need to investigate the root causes and for stringent preventative measures to be implemented by manufacturers.

Strengths and limitations of this study

- It is the first review to assess the problem of defective medicines in Canada.
- It quantifies and analyses drug recalls in Canada over a 9- year period.
- Clinical significance of the problem is undetermined, owing to the lack of data from Health Canada regarding adverse events associated with the use of defective medicines.

INTRODUCTION

Defective medicines are a major public health problem¹⁻⁴ Different surveys in lower income countries (LIC) and lower-middle-income countries (LMIC) have found that defective medicines are readily available.^{3, 5}

Defective medicine is a term used to describe any drug with a quality defect, whether the error was due to deliberate falsification or unintentional error during manufacturing.^{6, 7} It is a large category that comprises two main types of compromised drugs, substandard and falsified medicines. A substandard medicine is a medicine that does not meet the regulator standards due to an unintentional or negligent error.⁸ A falsified medicine, however, is one where deliberate and criminal intent is involved.⁸

In high income countries (HIC), there have been no studies with good methodological quality examining the overall prevalence of substandard or falsified medicines.³ [The surveillance system in HIC in Europe and North America, however, is a well-established system that has identified and withdrawn several medicines from the market with serious safety concerns.](#)^{9, 10} These surveillance systems have reported numerous incidents of substandard and falsified medicines, and highlighted the problem of such drugs in these countries. Examples of these are the falsified cancer drug, Avastin, and substandard spinal steroid injections reported in the USA.^{11, 12} In our previous study on the UK, we studied the problem of defective medicines in the UK by reviewing the drug alerts issued by the drug regulator over an 11-year period. The study showed that substandard medicines are [a problem that appears to be increasing.](#)⁷ We wished to explore another HIC and chose Canada, as the problem of

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3 defective medicines has never been explored in this setting and [because of the level of](#)
4 [data available in the public domain](#).
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7 In Canada, Health products are regulated by Health Canada, which is the federal
8 department responsible for the monitoring and regulating of medicines.¹³ It issues a
9 number of risk communication documents to the public and healthcare professionals.
10 These involve identification of the possible risk, assessment of its severity and
11 clarification of the nature of the problem. This communication is also initiated to
12 disseminate information regarding new safety issues of medicines or existing health
13 risks to allow healthcare professionals and their patients to make well-informed
14 decisions about their health.¹⁴
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21 The aim of this study was to explore the quality and safety of medicines in Canada by
22 analysing the risk communication documents conveying issues relating to defective
23 medicines.
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29 **METHODS**

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31 Health Canada uses 13 risk communication documents, which can be issued for the
32 public, healthcare professionals, and hospitals.¹⁴ A preliminary search for these risk
33 communication documents found that only five documents can be used by Health
34 Canada to convey any defective health product issue in the Canadian official supply
35 chain. These can be described as follows:
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- 40 • **Public Warning (PW):** issued by Health Canada if the use of the drug can
41 cause a severe adverse health consequence that may lead to death.
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- 44 • **Public Advisory (PA):** issued by Health Canada if exposure to or the use of
45 the drug can cause adverse health consequences, but is not life threatening
46 or serious.
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- 49 • **Healthcare Professional Communication - Notice to Hospitals (HPC-
50 NtoH):** to inform the healthcare professional about time-sensitive issues
51 concerning safety and/or efficacy of medicinal products. It is intended for
52 hospital use only.
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- **Healthcare Professional Communication - Dear Health Care Professional Letter (HPC-DHCPL):** to inform the healthcare professional about issues regarding safety and/or efficacy of medicinal products.
- **Health Product Recall (with type I, II or III):** These can be classified according to the urgency of the recall as follows:
 - Health Product Recall type I: issued if the health product can cause severe adverse health consequence that may lead to death.
 - Health Product Recall type II: issued if the exposure to or the use of the health product can cause adverse health consequences but is not life threatening or serious.
 - Health Product Recall type III: The exposure to or use of the health product is not likely to cause any harm but the recall is initiated for other reasons such as minor deviation from specifications.

Both PW and Health Product Recall type I are considered by Health Canada to be urgent communications, as they are issued for a medicine which may pose a serious health risk. PA, HPC-NtoH, HPC-DHCPL and type II and III Health Product Recalls are semi-urgent communications where the risk associated with the use of a medicine is not serious.¹⁴

A search for risk communication documents conveying issues relating to defective medicines (i.e., substandard and falsified medicines) was carried out. This was performed through the official Health Canada's website and using the search engine allocated for advisories, warnings, and recalls of health products (<http://www.hc-sc.gc.ca/dhp-mpps/medeff/advisories-avis/index-eng.php>). Health Canada started posting Health Product Recalls on its website in 2005. These recalls are the main tool that Health Canada uses to convey quality issues with medicines. Before that, there were only two types of risk communication documents (PA and HPC-DHCPL) available on Health Canada's website. We wanted to examine the same documents throughout the years. Therefore, the search was started from 2005, and all risk communication documents issued [between 1 January 2005 and 31 December 2013](#) were included. All risk communication documents (PW, PA, HPC-DHCPL, HPC-NtoH and Health Product Recalls) were reviewed and the relevant information was then extracted.

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3 All relevant information regarding defective health products was compiled and
4 exclusion criteria were as follows: veterinary medicines; medicines lacking efficacy or
5 [acquiring general safety issues](#); herbal and probiotic products; dietary and cosmetic
6 products; and other natural health product recalled for regulatory reason (i.e., those
7 do not have a valid marketing authorisation). The following data were extracted from
8 the risk communication documents: name, strength, and dosage form; year of the
9 document; nature of the defect; type of drug recall (in the case of Health Product
10 Recalls); and action to be taken by healthcare professionals or the public regarding
11 the defective medicine. In the case of Health Product Recalls and PW, the action is
12 to remove the defective medicine from the dispensary shelves and contact the
13 manufacturer for return. Whereas, with other risk communication documents where
14 there is no recall required, healthcare professionals and the public are given advice
15 on how to deal with defective medicines and to alert the public to be aware of
16 expected risks. Two types of drugs can be distinguished from risk communication
17 documents; substandard drugs and falsified drugs. The decision on which incident
18 was falsified or substandard is that published by Health Canada.
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30 The type of defects were then classified using the same classification as used in our
31 previous study.⁷ The quality defects were classified as contamination, minor or major
32 packaging defect, delivery (e.g., leaking bags) defect, stability failure, potency
33 issues, active ingredient defect and other issues (such as other deviations
34 concerning non-compliance with good manufacturing practice at manufacturing site).
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39 The WHO Organization Anatomical Therapeutic Chemical (ATC) Classification
40 System was used to classify defective medicines.¹⁵ The first level of this classification
41 categorises medicines according to the organ or system in which they act and the
42 second level classifies medicines according to their main therapeutic group. This
43 was performed to highlight the most frequent therapeutic classes affected by these
44 recalls.
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50 **Method of analysis**

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52 Minitab (version 16) software was used to store and analyse the data. Descriptive
53 statistics were used to summarise the results. Marketing authorisation holders of
54 recalled medicines were either licensed manufacturers or distributors. A comparison
55 between the manufacturers and distributors in the number of substandard medicines
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3 reported under each type of quality defect was carried out using Fisher's exact test.
4 A significant difference was defined at a p value <0.05. The comparison was
5 conducted to investigate if there are certain types of quality defects (e.g., stability or
6 packaging issues) that were more likely to be reported with distributors, as this may
7 indicate non-compliance with Good Distribution Practices.
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11 RESULTS

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13 A total of 653 defective medicines were identified in the Canadian supply chain
14 (Figure 1). Among these defective medicines, 649 were found to be substandard
15 medicines, and only four were found to be falsified medicines in the nine years
16 studied. The rate of reporting defective medicines has increased each year over the
17 last six years (Figure 2).
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23 Substandard medicines

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25 Substandard medicines represent the bulk of defective medicines ($n= 649$, 99%)
26 reported by Health Canada. The two most frequent types of defects reported were
27 stability ($n= 205$, 32%) and contamination ($n= 139$, 21%) issues (Table 1). It is clear
28 that substandard medicines with stability defects represent the largest group. The
29 majority of these formulations were found to have degraded one year after their
30 release into the market, resulting in low concentrations of active ingredients,
31 impurities, dissolution and disintegration failures. Tablets were the formulation most
32 frequently reported to be substandard (supplementary table 1).
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40 Among the 649 substandard medicines, 89 (14%) were subjected to urgent
41 communications and therefore required urgent recalls. These medicines were
42 reported using the Health Product Recall type 1 ($n= 87$) and the PW ($n=2$). More
43 than half of these medicines ($n= 46$, 53%) were parenteral formulations (Tables 2
44 and 3). Of the 89 medicines that were recalled, 34 were contaminated. The majority
45 of these were parenteral formulations that were recalled due to the presence of
46 particulate matters, the presence of microbes, or a lack of sterility assurance during
47 their manufacture (Table 2). The remaining substandard medicines ($n= 55$) were
48 urgently recalled due to other types of defects (Table 3), mainly packaging defects or
49 delivery issues (such as cracks in the vials or leaks in the bags, as well as faults in
50 the unit used to deliver the medicines). Packaging defects were one of the major
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3 clinical issues reported, and these included incorrect labelling (i.e., wrong drug
4 name, strength, or expiry date) and packaging that lacked important information
5 regarding safety or the use of medicines in the patient information leaflets. In some
6 cases, the labelling was correct, but the wrong medicines were filled, resulting in
7 major and urgent recalls of affected batches (Table 3).
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12 Other substandard medicines ($n= 560$, 86%) were subjected to semi-urgent recalls
13 ($n= 536$) or caution in use ($n= 24$). These were reported via the Health Product
14 Recall type II ($n= 288$ medicines, 44%) and III ($n= 245$, 38%), PA ($n= 8$, 1%), HPC-
15 NtoH ($n= 9$, 1%) and HPC-DHCPL ($n= 7$, 1%). Three medicines were recalled, but
16 the corresponding type of Health Product Recall was not given by Health Canada.
17 The majority of these drugs had stability, contamination and packaging defects
18 (supplementary table 2).
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25 Drugs that act on the nervous system ($n= 141$, 22%), alimentary tract and
26 metabolism ($n= 90$, 14%), and cardiovascular system ($n= 83$, 13%) were the
27 subgroups that most frequently contained substandard medicines. When the second
28 level of this classification (i.e., therapeutic classification) was used, the top three
29 groups reported to be substandard were analgesics ($n= 65$, 10%), antihypertensives
30 ($n= 50$, 8%) and antibacterials ($n= 38$, 6%) (supplementary table 3).
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38 **Substandard medicines categorised by manufacturers**

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40 The review identified 122 licensed manufacturers and 26 licensed distributors.
41 Manufacturers held the marketing authorisation for 611 substandard medicines and
42 distributors for 38 (Table 4). No unlicensed manufacturers or distributors were
43 involved. A comparison between those manufacturers and distributors in the number
44 of substandard medicines reported under each defect type and the p values for
45 these differences is presented in Table 4. No significant differences were observed
46 between manufacturers and distributors.
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53 The top 20 manufacturers are listed in supplementary table 4. It was noted that 50%
54 or more of substandard medicines manufactured by Apotex Inc., Pfizer Canada Inc.
55 and Laboratoire Riva Inc. had stability issues. Almost half of the substandard
56 products from Baxter Co., Hospira Healthcare Co. and GlaxoSmithKline Inc. were
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3 contaminated. Products of Sandoz Canada Inc. had a problem with the active
4 ingredient; **the concentration was either too high or too low**. More than half of
5 Novartis products, which are reported to be substandard, were recalled due to
6 delivery concerns, such as failure of the child-resistant feature of the bottle cap or
7 leaks in the infusion bags.
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11 12 13 14 **Falsified medicines** 15

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17 Four incidents of falsified medicines were identified in Canada's supply chain
18 between 2011 and 2013. All these incidents involved two sexual enhancement
19 medicines, Viagra® (sildenafil) and Cialis® (tadalafil).
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23 In all cases of falsified medicines, Public Advisories were issued to inform the public
24 to contact their healthcare professionals if they had concerns about these falsified
25 medicines. The public was also advised to verify that these products were assessed
26 by Health Canada for safety by looking at the authorisation number printed on the
27 label. These medicines were seized in the retail outlets in Canada, and no further
28 information was given by Health Canada about the subsequent investigation or
29 action taken by Health Canada.
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38 **DISCUSSION** 39

40 This is the first review that discusses the issue of substandard and falsified
41 medicines in Canada by evaluating the risk communication documents and drug
42 recalls posted on Health Canada website. Our observations of defective medicines
43 recalls over nine consecutive years, from 2005 to 2013, have shown that the recall of
44 substandard medicines is an increasing trend. It is concerning that over half of the
45 stability failures were related to instability of active ingredients or dissolution and
46 disintegration failure. Both defects have the potential to affect the bioavailability of
47 the active ingredients in the systemic circulation, and in turn, may lead to therapeutic
48 failure.
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Substandard medicines

The most frequent type of formulation reported to be substandard were tablets. Tablets have a slow onset of action and require less precaution in terms of sterility, than parenteral formulations. The extent of adverse consequences that can arise from failure to comply with manufacturing requirements, however, cannot be ignored. This was evident from the death of 120 patients in Pakistan due to contamination of isosorbide mononitrate tablets with large doses of an antimalarial drug.¹⁶ Another of the most pronounced examples is the phenobarbital and morphine tablet recalls in Canada. Oversized tablets (i.e. tablets that exceed the weight requirement) were found in both drugs, raising the risk of the patients taking as much as double the strength stated on the bottle (Table 3). The Institute for Safe Medication Practices (ISMP), a non-profit organisation, stated that the US manufacturer (KV Pharmaceutical) received abnormally high reports of serious adverse events concerning overdose of these recalled tablets.¹⁷ However, owing to the lack of sufficient details, it was impossible to link the overdose events specifically to the substandard tablets. The Adverse events relating to this defect have not been documented by Health Canada.

It was uncertain whether the rise of substandard medicines incidents were related to improved detection by Health Canada or due to an increase of substandard medicine production by manufacturers. The rate of increased incidence of substandard medicines could be associated with the implementation of improved detection policies and regulations by Health Canada. Introduction of Good Manufacturing Practices (GMP) inspection policy for Canadian drug establishments may be one of the explanations.¹⁸ Since 1996, there have been numerous changes in GMP guidelines and international agreements. These led Health Canada to update its policy on GMP inspection in January 2008 as a response to harmonise its GMP compliance programme with drug regulatory authorities in other countries.¹⁸ Subsequently, there has been a steady increase of incidents of substandard medicines from 2008 to 2013 (Figure 2). Similarly, it has been highlighted that most of the FDA recalls were related to FDA inspectors' visits in the USA.¹⁹

The GMP policy illustrates the procedures Health Canada follows to ensure that all drug establishments comply with GMP guidelines. This is conducted via inspections

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3 with varying cycles according to a risk-based approach to assess complaints about
4 medicines, and a ranking scale of priority.¹⁸ This assessment is to ensure that these
5 complaints are dealt with in a timely manner. The performance of Health Canada in
6 using the risk-based approach, however, was criticised in the 2011 report of the Auditor
7 General of Canada.²⁰ Based on a representative sample (50) of the files that Health
8 Canada received in 2009 and 2010 concerning drug-related complaints, only 27 were
9 dealt with according to the established risk-based standard operating procedures for
10 prioritising reported complaints. The report concluded that Health Canada did not
11 consistently apply its risk-based approach and therefore some of these complaints
12 might not be processed in a timely manner proportional to their expected risk.²⁰
13 Therefore, the possibility that the increase in substandard medicines was a result of
14 poor manufacturing practices cannot be excluded.
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24 **Manufacturing errors and investigation of the root cause**

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26 It is the responsibility of the manufacturers and marketing authorisation holders to recall
27 their substandard products after consultation with Health Canada. The majority of these
28 recalls were issued by the manufacturers or marketing authorisation holders using the
29 Health Product Recall type I, II and III, which accounted for 95% of the total
30 substandard medicines reported. Stability issues were mainly identified by the
31 manufacturers during on-going stability testing. However, it is unknown whether these
32 defects were identified by internal auditing systems of the manufacturers, by
33 intervention of the Health Canada inspection team or by reports from healthcare
34 professionals.
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42 Analysing pharmaceutical product recalls can be of great importance to identify the root
43 causes of recalled medicines. The prompting of a drug recall can be regarded as a
44 disastrous failure of the manufacturer's quality plan. Even with stringent quality
45 measures, errors can occur.^{21, 22} Thus, it is very important to identify the root cause of
46 the defects to avoid similar episodes in the future. The root cause for a defect is
47 required to be submitted to Health Canada, as soon as it is identified, along with other
48 information relating to the quantity and depth of the distribution of the affected
49 medicine. It is the responsibility of Health Canada to monitor the overall procedure and
50 assess the root cause for this problem and, if required, to conduct an inspection to
51 verify that a corrective action is implemented.^{23, 24} It has been highlighted in this review
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3 that stability failure and contamination issues were the defect types being reported
4 most frequently. These issues affected several manufacturers on more than one
5 occasion (supplementary table 4). This highlights the need for root cause investigations
6 and appropriate measures to be implemented by manufacturers [as well as effective](#)
7 [monitoring by Health Canada.](#)
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10 11 **Falsified medicines**

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14 Only four incidents of falsified medicines were reported by Health Canada. The
15 detection is extremely low compared with substandard medicine. Health Canada has
16 robust GMP inspections that cover all drug establishments including manufacturers,
17 distributors and wholesalers. The reporting system of Health Canada is concerned
18 with falsified medicines detected within the scope of GMP inspections.¹⁸ Some
19 falsified medicines may be intercepted and seized by enforcement bodies on their
20 way to target destinations, but not necessarily intended for the Canadian market.
21 This may explain the low detection rate by Health Canada.
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28 29 **Comparison with the UK**

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31 [Despite the fact that Canada and the UK represent 2% \(for each\) of the global](#)
32 [pharmaceutical market volume, they are two of the top markets by value of marketed](#)
33 [medicines.](#) Canada and the UK hold equal global pharmaceutical market share
34 values of USD \$21,877 and USD \$21,635 billion, respectively.²⁵ They also use
35 similar approaches in dealing with substandard medicines based on the expected
36 risk. In the UK, the drug regulator uses four classes of drug alerts to communicate
37 the risk of substandard medicines to Healthcare professionals.⁶ A request to recall
38 the affected batches is issued with the first three classes (class 1-3 drug alerts),
39 comparable to the Health Product recall type I, II and III issued by Health Canada. A
40 class 4 drug alert is issued by the UK drug regulator when a drug recall is not
41 required, but caution is needed to deal with a substandard medicine. This type of
42 communication is similar to the PA, HPC-NtoH and HPC-DHCPL used by Health
43 Canada. A class 1 drug recall (issued in the UK), and both the Health Product recall
44 type I and PW (issued in Canada) are considered to be urgent communications. The
45 rest of the documents in both countries are deemed as semi-urgent
46 communications.^{6, 14}
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3 Out of the 280 substandard medicines found in the UK, 17 (6%) were subject to
4 urgent communication.⁷ The corresponding number in Canada was 89 (14%) out of
5 649. Overall, a larger number of substandard medicines were found in the Canadian
6 supply chain (649 medicines) than in the UK (280 medicines).⁷ It is also important to
7 mention that the UK study was conducted over a longer period (i.e., 11 years) than
8 the one on Canada (i.e., 9 years). Therefore, the difference in the number of
9 substandard medicines may be even larger than it appears. The major contributor to
10 this difference in our data was the number of medicines recalled due to stability
11 problems (Figure 3), which were responsible for 50% of the difference. The
12 differences in stability issues between Canada and the UK require further
13 investigation.
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21 22 **Limitations**

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24 This study encountered some limitations. The expected adverse events associated
25 with the use of substandard medicines were not reported by Health Canada or the
26 manufacturers. Moreover, the adverse reaction database does not state the batch
27 numbers of medicines reported with the complaint. Therefore we could not compare
28 the expected risk associated with the recalled batches of substandard medicines
29 with the adverse drug reaction database. Thus, the clinical significance of the
30 problem is unknown.
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39 40 **CONCLUSION**

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42 Substandard medicines are a problem in Canada and have resulted in an increasing
43 number of recalled medicines. Most of the failures were related to stability issues,
44 raising the need to investigate the root causes and for stringent preventative
45 measures to be implemented by manufacturers. Regular GMP inspections on
46 manufacturing sites were highlighted in this review as some of the most important
47 tools that can improve detection of substandard medicines.
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52 53 **Contributors:**

54 TA and IC conceived the study design and planned the research. TA performed the
55 database search, extracted the data and drafted the manuscript. HS double-checked
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3 the extracted data, and interpreted the results. IC and HS edited and reviewed the
4 manuscript. All authors approved the final version of the manuscript.
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8 **Competing interests:** None.
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11 **Funding:** This research received no specific grant from any funding agency in the
12 public, commercial or not-for-profit sectors.
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16 **Ethical approval:** Not required.
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20 **Data sharing:** No additional data available.
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TABLES:

Table 1: Substandard medicines

Defect Type	Number of medicines	%	Defect details	Number of medicines
Stability defects	205	32	Concern about stability of active ingredients	63
			Levels of impurities in excess of specification at different time points	50
			Dissolution, disintegration and drug release failure	45
			Others	47
Contamination	139	21	Impurities	82
			Lack of sterility assurance	35
			Microbial contamination	22
Minor packaging defects	71	11	Fault involving the external packaging or minor printing errors that do not involve name or strength of a medicines	60
			Missing or incorrect product registration number, batch number, manufacturer's name or expiry date	11
Major packaging defects	65	10	Missing or incorrect name ,strength, or active ingredient of a medicine on carton or box	35
			Packing a medicine in the wrong carton or present of a foreign tablet or capsule in the bottle or blister	30
Defects in active ingredient	62	10	Excessive amount of active ingredients	26
			Inadequate amount of active ingredient	20
			Active ingredient is out of specification	16
Delivery defects	35	5	Fault with a device	22
			Leakage or loose/ tight seal ,cracks in a vial or broken tablets	9
			Others	4
Other defects	72	11	GMP deficiencies and deviation from preapproved specifications	48
			Inappropriate shipment	14
			Dissolution / disintegration failure	10
Total	649	100		649

Table 2: Contaminated medicines subjected to urgent recalls (Health Product Recall type I).

Medications (number of incidents)	Formulation	Defect description
Marcaine (2), acyclovir (1), nitroglycerin (1), magnesium sulfate (1), dexamethasone sodium (1), vistide (1) and carboplatin (1)	Solution for injection	Visible particulates were identified in the formulation (such as white, metallic or glass particles.)
Propofol (4) and fat emulsion (1)	Emulsion for injection	
Extraneal (1) ciprofloxacin (1), carmustine (1), technetium Tc 99m (1) and liposomal amphotericin B (1)	Solution for injection	Microbial contamination (bacterial, fungal or viral contamination)
Docusate sodium (1)	Capsules	
Sucrose (1)	Oral liquid	
Benzalkonium chloride (1)	Topical Liquid	
Sodium Chloride (1) and dextrose (1)	Solution for injection	Integrity of the foil seal is compromised leading to potential contamination of the vial adapter
Diameal (1), DTE technetium Tc 99m (1), electrolyte infusion (1) and dextrose (1)	Solution for injection	Lack of sterility assurance at the time of manufacture
Gen Teal Artificial Tears (1)	Ophthalmic Solution	
Heparin sodium (3)	Solution for injection	Contamination with heparin-like contaminant
Quetiapine (3)	Tablets	cross-contamination of trace amounts of clindamycin in quetiapine active pharmaceutical ingredient during the manufacturing process

Note: All medicines were reported using health Product Recall Type I document

Table 3: Substandard medicines subjected to urgent recalls (Health Product Recall type I and PW) with other defect types

Type of defect	Medications (number of incidents)	Formulation	Defect description
Major packaging defects (incorrect labelling)	Trazodone (1), amlodipine (1) and fluvoxamine (1)	Tablets	Some products contained the wrong medicines due to labelling errors (e.g., amlodipine instead of minocycline, minocycline instead of amlodipine, clonazepam instead of rifampicin and fluphenazine instead of Octreotide) or filling errors (e.g., nabilone instead of trazodone, ciprofloxacin instead of fluvoxamine, trazodone instead of nabilone, Isoproterenol instead of morphine and blue collyrium instead of prednisolone)
	Nabilone (1), minocycline (1) and rifampicin (1)	Capsules	
	Morphine sulphate (1) and octreotide acetate omega (1)	Solution for injection	
	Prednisolone (1)*	Ophthalmic solution	
	Hemodialysis acid concentrates (1), remifentanil HCl (1), pamidronate disodium (1), tobramycin (1) and triamcinolone acetonide (1)	Solution for injection	Wrong strength , dosage or expiry date were printed on the packaging
	Sodium solysterene sulfonate (1)	Suspension	
	Acetaminophen (1)	Suppositories	
	Personnelle cold and flu tablets (2), acetylsalicylic acid (1), acetaminophen (1) and Personelle acid control (1)	Tablets	Important mandatory warning statement was missed on the external packaging
	Oral contraceptive pills (4)	Tablets	Additional placebo tablet was found in place of an active tablet in one blister pack raising the risk of unwanted pregnancy
Ibuprofen (2)	Tablets	The label stated that the bottle had a child resistant cap, but the cap used was not child resistant.	
Stability defects	Smallpox vaccine (1)	Solution for injection	Evidence of instability based on its appearance.
	Timolol (1)	Ophthalmic Solution	Active ingredient was out of specification after 12 month of production date
	Valproic acid (1)	Capsules	Disintegration test failure within the shelf life of the drug
	Amoxicillin (1)	Suspension	Out of specification assay result was obtained at various time points.
Active ingredients defects	Phenobarbital (1)* and morphine SR (1)	Tablets	Oversized tablets were found raising the risk of overdose
	Acetylsalicylic acid (1)		Inadequate amount of active ingredient
	Delflex (1) and carmustine (1)	Solution for injection	Excessive amount of active ingredients
	Ethacrynic acid (1)		Inadequate amount of active ingredient
Delivery defects	Paliperidone palmitate (1), nutrinal (1), degarelix (1), caspofungin acetate (1), vancomycin (1) and argatroban (1)	Solution for injection	Cracks in the syringes or vials , or leaks from the bags were identified raising the risk of contamination
	Sumatriptan (1)		Pre-filled syringes were filled with needles that protruded through the needle shield
	Morphine sulphate (1)		Plunger friction with the vial may cause pump occlusion or delivery of inaccurate dose
	Cough and Cold syrup (9)	Syrup	The child-resistant feature of the bottle cap was not functioning properly
Other	Hypromellose (1)	lubricant eye gel	Non-compliance with Good manufacturing practices

*Medicine was reported using the Public Warning document. Others were reported using Health Product Recall type I

Table 4: Substandard medicines categorised by type of marketing authorisation holders

Type of quality defect	Medicines marketed by manufacturers (n = 122)	Medicines marketed by distributors (n = 26)	P-Value*
	Number of medicines, (%)	Number of medicines, (%)	
Stability	191 (31)	14 (37)	0.476
Contamination	134 (22)	5 (13)	0.228
Minor packaging	69 (11)	2 (5)	0.417
Major packaging	60 (10)	5 (13)	0.573
Active ingredient	59 (10)	3 (8)	1.000
Delivery	34 (5)	1 (3)	0.714
Others	64 (11)	8 (21)	0.058
Total	611 (100)	38 (100)	

*A significant difference was defined at a p value <0.05.

Figure legends:

Figure 1: Flow diagram of search and resulting incidents.

Figure 2: Number of incidents of defective medicines reported by Health Canada.

Figure 3: Comparison between Canada and the UK in the types of substandard medicines.

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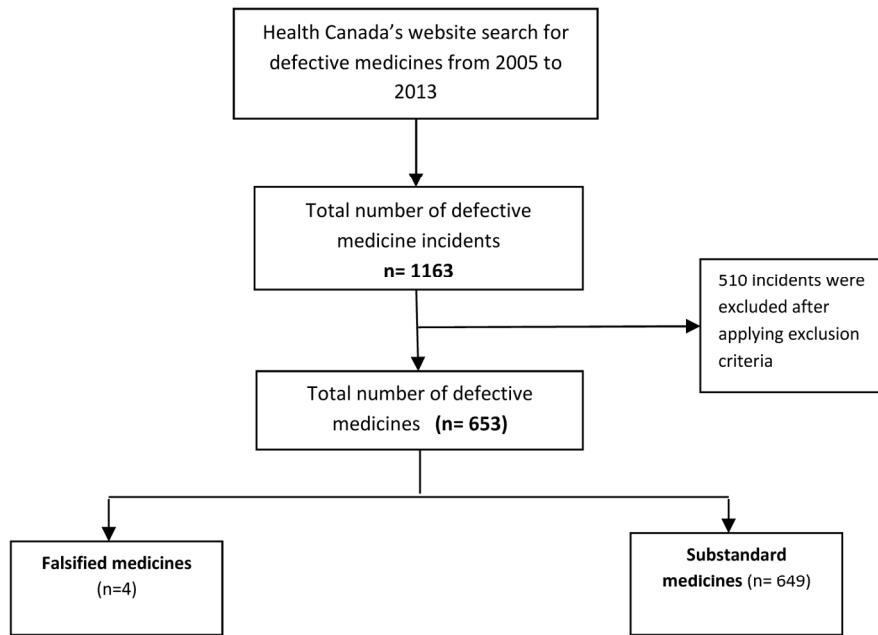


Figure 1: Flow diagram of search and resulting incidents.
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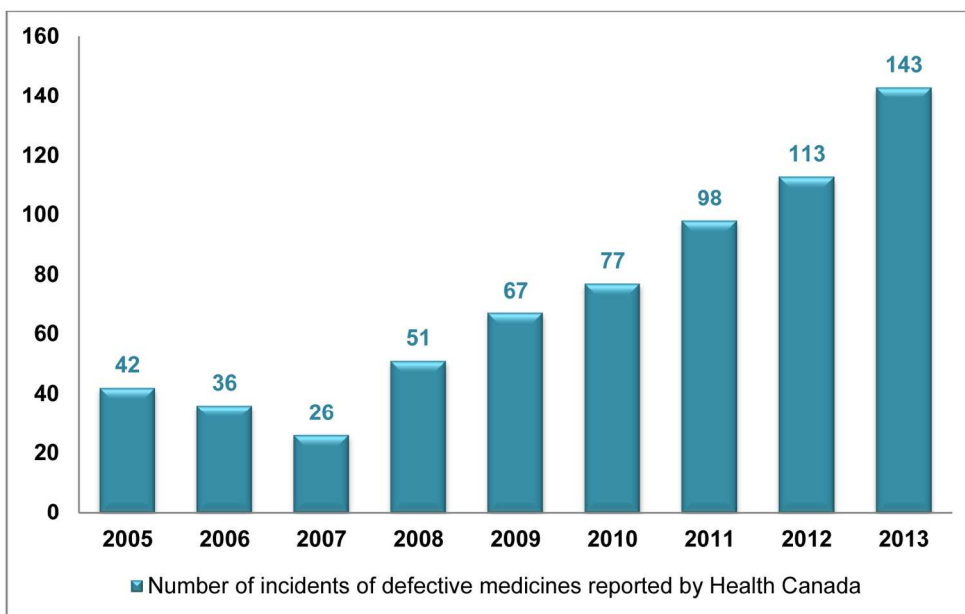


Figure 2: Number of incidents of defective medicines reported by Health Canada.
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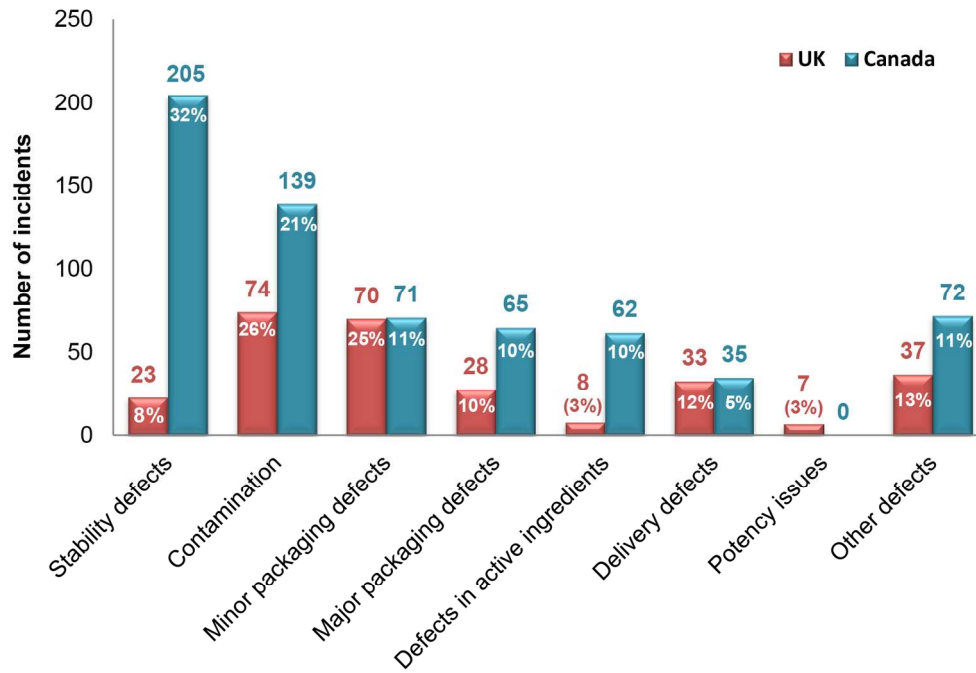


Figure 3: Comparison between Canada and the UK in the types of substandard medicines reported. Percentages are given based on the total number of incidents reported in each country.
151x103mm (300 x 300 DPI)

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Supplementary data:**Table 1: Number of formulations under each defect type of substandard medicines**

Defect Type	Formulation type	Number of formulations
Stability defect	Tablets	89
	Parenteral	46
	Topical preparations	34
	Capsules	24
	Liquid preparations	12
Contamination	Parenteral	71
	Tablets	29
	Topical preparations	21
	Liquid preparations	11
	Capsules	7
Minor packaging defect	Tablets	39
	Parenteral	14
	Capsules	9
	Liquid preparations	5
	Topical preparations	4
Major packaging defects	Tablets	35
	Parenteral	13
	Capsules	11
	Topical preparations	6
Defect in active ingredient	Tablets	18
	Topical preparations	16
	Parenteral	13
	Liquid preparations	8
	Capsules	6
Delivery defect	Parenteral	11
	Liquid preparations	10
	Topical preparations	8
	Tablets	6
	Capsules	1
Other defects	Tablets	35
	Parenteral	20
	Topical preparations	11
	Liquid preparations	3
	Capsules	3
Total		649

Table 2: Substandard medicines subjected to semi-urgent communications (Health Product Recall - Types II and II, PA, HPC-NtoH and HPC-DHCPL)

Type of defect	Health Product Recalls - type II	Health Product Recalls - type II	PA	HPC-NtoH	HPC-DHCPL	Type of drug recall was not stated
Stability defects	90	107	0	0	1	0
Contamination	68	25	1	6	2	0
Minor packaging defects	22	47	0	2	0	0
Defects in active ingredient	33	22	0	0	1	1
Major packaging defects	23	12	1	1	0	1
Delivery defects	10	6	5	0	2	0
Other issues	42	26	1	0	1	1
Total	288	245	8	9	7	3

PA: Public Advisory; **HPC-DHCPL:** Healthcare Professional Communication - Dear Health Care Professional Letter; **HPC-NtoH:** Healthcare Professional Communication - Notice to Hospitals

Table 3: Substandard medicines reported by Health Canada, classified according to the organ or system in which they act and according to the therapeutic subgroup they belong (Classification ATC) 2005-2013:

Category	No.	%	Category	No.	%
According to organ or system in which the drug acts			According to subgroup, therapeutic main group		
Nervous system	141	21.7	Analgesics Psycholeptics Psychoanaleptics Anaesthetics Antiepileptics Anti-parkinson drugs	65 26 18 15 13 4	10.0 4.0 2.8 2.3 2.0 0.6
Alimentary tract and metabolism	90	13.9	Drugs for acid related disorders Vitamins Mineral supplements Laxatives Drugs used in diabetes Drugs for constipation Stomatological preparations	25 22 16 12 9 3 3	3.9 3.4 2.5 1.8 1.4 0.5 0.5
Cardiovascular System	83	12.8	Antihypertensives Lipid modifying agents Cardiac therapy	50 24 9	7.7 3.7 1.4
Anti-infectives for systemic use	65	10.0	Antibacterials for systemic use Antimycotics for systemic use Immune sera and immunoglobulins Vaccines Antivirals for systemic use	38 8 8 6 5	5.9 1.2 1.2 0.9 0.8
Blood and blood forming organs	63	9.7	Blood substitutes and perfusion solutions Antithrombotic agents Antianemic preparations	30 19 14	4.6 2.9 2.2
Dermatologicals	46	7.1	Corticosteroids, dermatological preparations Other dermatological preparations Anti-acne preparations Antifungals for dermatological use	18 14 9 5	2.8 2.2 1.4 0.8
Respiratory system	31	4.8	Antihistamines for systemic use Cough and cold preparations Drugs for obstructive airway diseases Nasal preparations	11 11 7 2	1.7 1.7 1.1 0.3
Genito-urinary system and sex hormones	29	4.5	Sex hormones and modulators of the genital system Urologicals Gynecological antiinfectives and antiseptics	22 5 2	3.4 0.8 0.3
Antineoplastic and immunomodulating agents	28	4.3	Antineoplastic agents Immunosuppressants Immunostimulants Endocrine therapy	18 4 4 2	2.8 0.6 0.6 0.3
Various	26	4.0	Diagnostic radiopharmaceuticals All other therapeutic products Contrast media	20 4 2	3.1 0.6 0.3
Sensory organs	21	3.2	Ophthalmologicals Otolologicals	20 1	3.1 0.2
Musculo-skeletal system	18	2.8	Antiinflammatory and antirheumatic products Drugs for treatment of bone diseases Muscle relaxants	11 6 1	1.7 0.9 0.2
Systemic hormonal preparations, excluding sex hormones and insulins	8	1.2	Pituitary and hypothalamic hormones and analogues Pancreatic hormones Pituitary and hypothalamic hormones and analogues	3 3 2	0.5 0.5 0.3
Total	649	100	Total	649	100

Table 4: Substandard medicines categorised by manufacturers and type of defects

Manufacturer*	Number of medicines under each type of quality defect							Total	Percentage	Total number of medicines marketed by each manufacturer in Canada
	Stability	Contamination	Minor packaging	Active ingredient	Major packaging	Delivery	Others			
Apotex Inc.	31	13	4	2	2	2	3	57	9	220
Teva Canada Ltd.	15	11	5	7	10	2	3	53	8	224
Pharmascience Inc.	12	3	3	6	6	2	3	35	5	173
Vita Health Products Inc.	4	0	14	4	10	1	0	33	5	NA
Sandoz Canada Inc.	5	8	1	12	5	0	0	31	5	232
Hospira Healthcare Co.	1	13	0	0	0	3	9	26	4	94
Novartis Pharmaceuticals Canada Inc.	4	2	1	1	1	13	1	23	4	114
Pfizer Canada Inc.	10	2	4	1	1	1	1	20	3	120
GlaxoSmithKline Inc.	3	8	2	6	0	1	0	20	3	77
Baxter Co.	2	8	4	0	1	1	0	16	2	58
Sanofi-Aventis Canada Inc.	4	1	2	5	0	0	4	16	2	76
Laboratoire Riva Inc	11	1	0	0	0	0	1	13	2	NA
Pro-Doc Ltd.	5	3	0	0	1	0	3	12	2	158
Mylan pharmaceuticals	0	0	2	1	4	1	3	11	2	145
Pharmetics Inc.	1	3	0	0	0	0	2	10	2	NA
JAMP Pharma Co.	4	1	1	3	0	0	1	10	2	37
Pharmaceutical Partners of Canada.	2	3	0	0	1	1	2	9	1	40
Schering-Plough Canada Inc.	3	1	2	0	0	0	2	8	1	72
McNeil Consumer Products Co.	0	2	1	0	0	0	5	8	1	28
Taro Pharmaceuticals Inc.	3	3	0	0	0	0	1	7	1	21
								418	64	

*Only the top 20 manufacturers are listed.