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

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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.

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

The WHO Organization Anatomical Therapeutic Chemical (ATC) Classification System was used to classify the total number of defective medicine incidents obtained.[13] The first two levels of this classification were used.

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 (649 medicines, 99%) reported by Health Canada. The two most frequent types of defects reported were stability (205 incidents) and contamination (139 incidents) issues (Table 1). Stability of formulations was a significant problem. 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 were subjected to urgent recalls. More than half of these medicines (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 (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).

Drugs that act on the nervous system (141/649), alimentary tract and metabolism (90/649), and cardiovascular system (83/649) 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 (65/649), antihypertensives (50/649) and antibacterials (38/649) (supplementary table 2).

Substandard medicines categorised by manufacturers

The review identified 148 manufacturers that were holding the marketing authorisation for 649 recalled medicines. All manufacturers that held the marketing authorisation of 8 or more recalled medicines are listed in supplementary table 3. 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 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

Canada. Oversized tablets (i.e. tablets that exceed the weight requirement) were found in both drugs, raising the risk of the patients to have 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.[15] 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 can be correlated with the implementation of improved detection policies and regulations by Health Canada. Introduction of GMP inspection policy for Canadian drug establishments may be one of the explanations.[16] In January 2008, Health Canada introduced this policy as a response to increasing demand to update its policy on GMP, given that so many GMP guidelines and international agreements had been made since 1996. Subsequently, there has been a steady increase of incidents of substandard medicines from 2008 to 2013 (Figure 2). This policy illustrates the procedures that the Health Products and Food Branch (HPFB) follows to ensure that manufacturing sites, distributers and wholesalers are complying with GMP. It is conducted via inspections by the HPFB inspectorate with varying cycles, which depend on an approach that takes risk assessment into consideration, and a ranking scale of priority.[16] Similarly, it has been highlighted that most of the FDA recalls were related to FDA inspectors' visits in the USA.[17]

Canada and the UK are two of the top pharmaceutical markets in the world, holding equal global pharmaceutical market share values of USD $21,877 and USD $21,635 billion, respectively.[18] A larger number of substandard medicines were found in the Canadian supply chain (649 medicines) than in the UK (280 medicines).[7] The major contributor to this difference in our data was the number of medicines recalled due to stability problems (Figure 3), which were responsible for 50% of the difference. The differences in stability issues between Canada and the UK require further investigation.

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

accounted for 95% of the total recalls. Stability issues were mainly identified by the manufacturers during on-going stability testing. However, it is unknown whether these defects were identified by internal auditing systems of the manufacturers, by intervention of the Health Canada inspection team or by reports from healthcare professionals.

Analysing pharmaceutical product recalls can be of great importance to identify the root causes of recalled medicines. The prompting of a drug recall can be regarded as a disastrous failure of the manufacturer's quality plan. Even with stringent quality measures, errors can occur.[23,24] Thus, it is very important to identify the root cause of the defects to avoid similar episodes in the future. It has been highlighted in this review that stability failure and contamination issues were the defect types being reported most frequently. These issues affected several manufacturers on more than one occasion (supplementary table 3). This highlights the need for root cause investigations and appropriate measures to be implemented by manufacturers.

Limitations

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

CONCLUSION

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. Regular GMP inspections on

manufacturing sites were highlighted in this review as some of the most important tools that can improve detection of substandard medicines.

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.

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Ethical approval: Not required.

Data sharing: No additional data available.

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TABLES AND FIGURES

Figure 1: Flow diagram of search and resulting incidents

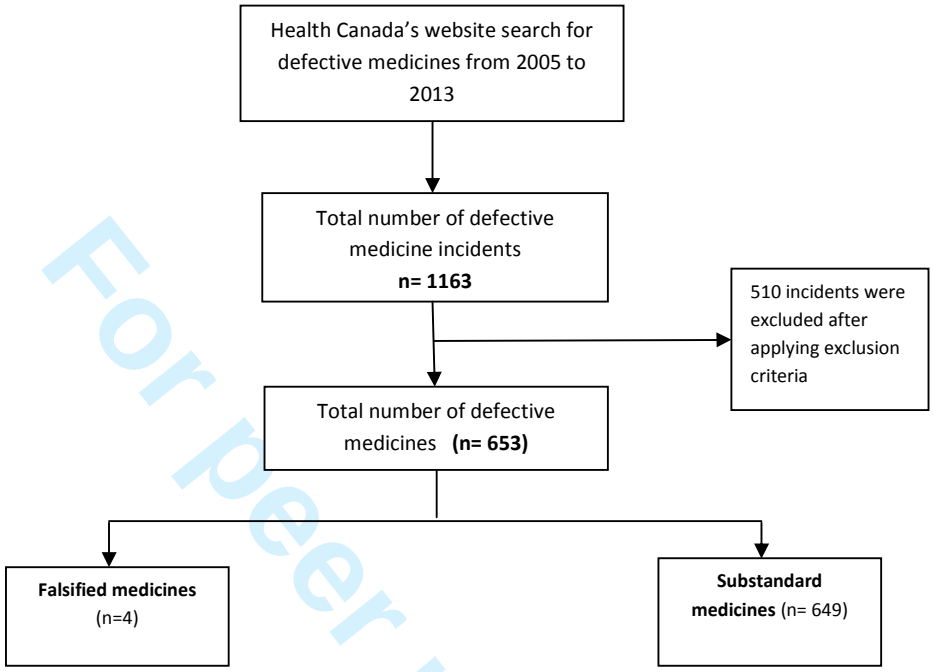

Figure 2: Number of incidents of defective medicines reported by Health Canada

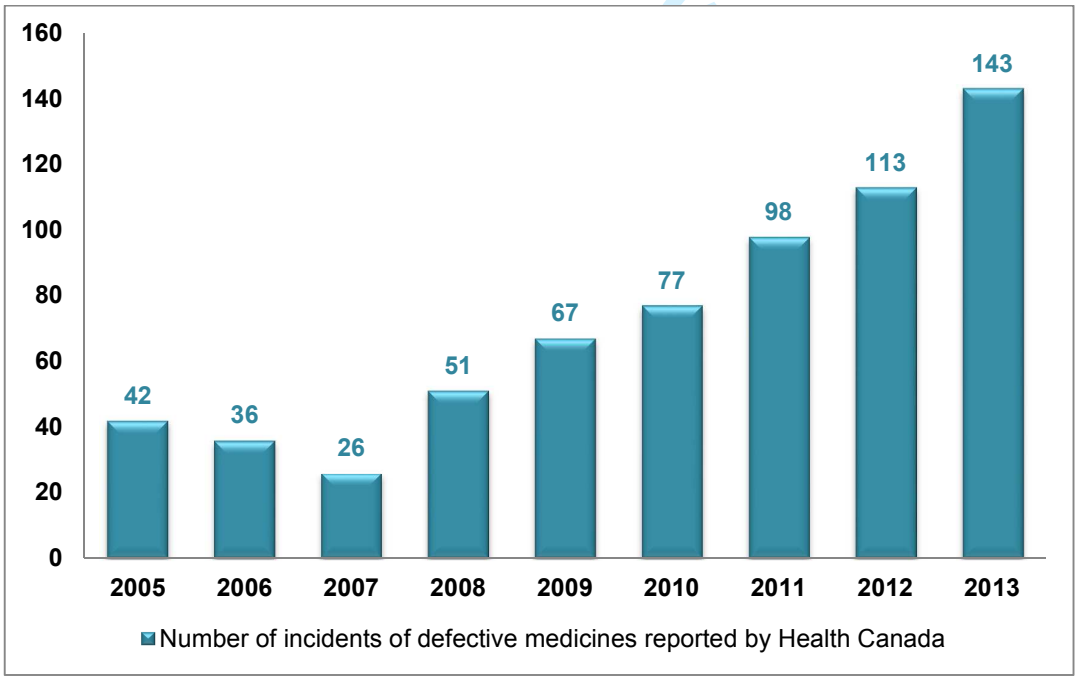

Figure 3: Comparison between Canada and the UK in the types of substandard medicines.

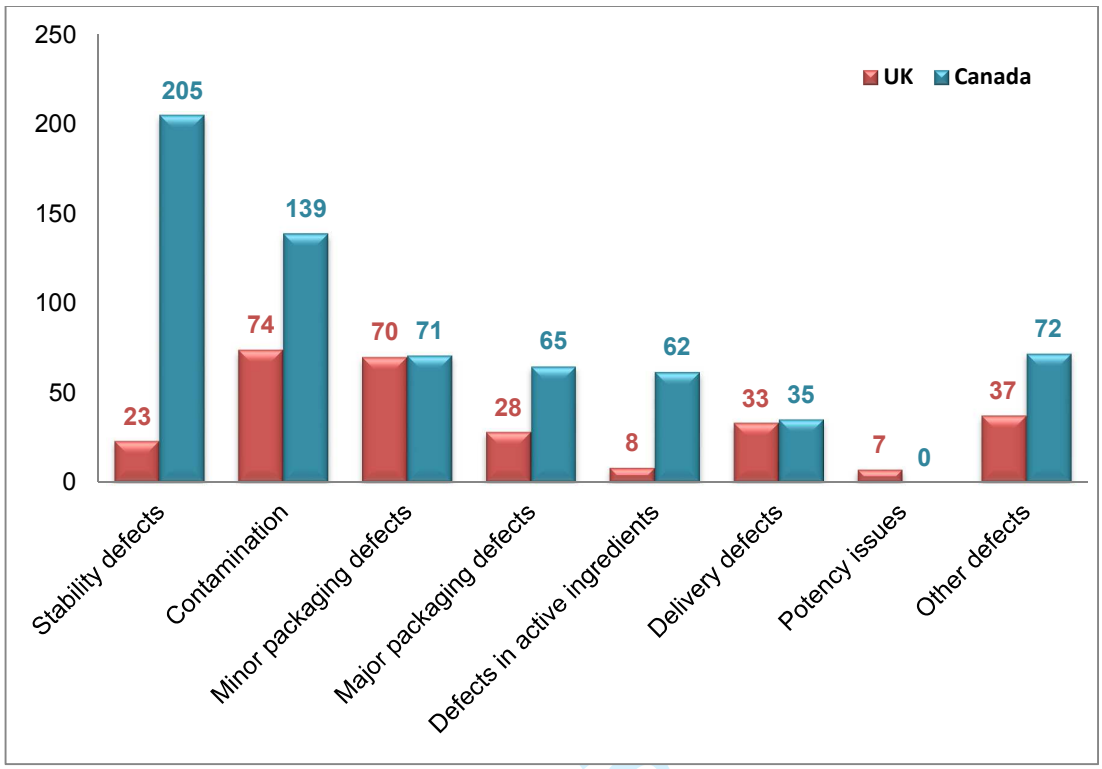

Table 1: Substandard medicines

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 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 aoncentrates (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), nutrineal (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

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	65	10.0
			Psycholeptics	26	4.0
			Psychoanaleptics	18	2.8
			Anaesthetics	15	2.3
			Antiepileptics	13	2.0
			Anti-parkinson drugs	4	0.6
Alimentary tract and metabolism	90	13.9	Drugs for acid related disorders	25	3.9
			Vitamins	22	3.4
			Mineral supplements	16	2.5
			Laxatives	12	1.8
			Drugs used in diabetes	9	1.4
			Drugs for constipation	3	0.5
			Stomatological preparations	3	0.5
Cardiovascular System	83	12.8	Antihypertensives	50	7.7
			Lipid modifying agents	24	3.7
			Cardiac therapy	9	1.4
Anti-infectives for systemic use	65	10.0	Antibacterials for systemic use	38	5.9
			Antimycotics for systemic use	8	1.2
			Immune sera and immunoglobulins	8	1.2
			Vaccines	6	0.9
			Antivirals for systemic use	5	0.8
Blood and blood forming organs	63	9.7	Blood substitutes and perfusion solutions	30	4.6
			Antithrombotic agents	19	2.9
			Antianemic preparations	14	2.2
Dermatologicals	46	7.1	Corticosteroids, dermatological preparations	18	2.8
			Other dermatological preparations	14	2.2
			Anti-acne preparations	9	1.4
			Antifungals for dermatological use	5	0.8
Respiratory system	31	4.8	Antihistamines for systemic use	11	1.7
			Cough and cold preparations	11	1.7
			Drugs for obstructive airway diseases	7	1.1
			Nasal preparations	2	0.3
Genito-urinary system and sex hormones	29	4.5	Sex hormones and modulators of the genital system	22	3.4
			Urologicals	5	0.8
			Gynecological antiinfectives and antiseptics	2	0.3
Antineoplastic and immunomodulating agents	28	4.3	Antineoplastic agents	18	2.8
			Immunosuppressants	4	0.6
			Immunostimulants	4	0.6
			Endocrine therapy	2	0.3
Various	26	4.0	Diagnostic radiopharmaceuticals	20	3.1
			All other therapeutic products	4	0.6
			Contrast media	2	0.3
Sensory organs	21	3.2	Ophthalmologicals	20	3.1
			Otologicals	1	0.2
Musculo-skeletal system	18	2.8	Antiinflammatory and antirheumatic products	11	1.7
			Drugs for treatment of bone diseases	6	0.9
			Muscle relaxants	1	0.2
Systemic hormonal preparations, excluding sex hormones and insulins	8	1.2	Pituitary and hypothalamic hormones and analogues	3	0.5
			Pancreatic hormones	3	0.5
			Pituitary and hypothalamic hormones and analogues	2	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	

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

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Quality of medicines in Canada: a retrospective review of risk 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 problem.[1-4] 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.

In Canada, Health products are regulated by Health Canada, which is the federal department responsible for the monitoring and regulating of medicines.[13] 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 also initiated to disseminate information regarding new safety issues of medicines or existing health risks to allow healthcare professionals and their patients to make well-informed decisions about their health.[14]

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

METHODS

Health Canada uses 13 risk communication documents, which can be issued for the public, healthcare professionals, and hospitals.[14] A preliminary search for these risk communication documents found that only five documents can be used by Health Canada to convey any defective health product issue in the Canadian official supply chain. These can be described as follows:

- **Public Warning (PW):** issued by Health Canada if the use of the drug can cause a severe adverse health consequence that may lead to death.
- **Public Advisory (PA):** issued by Health Canada if exposure to or the use of the drug can cause adverse health consequences, but is not life threatening or serious.
- **Healthcare Professional Communication - Notice to Hospitals (HPC-NtoH):** to inform the healthcare professional about time-sensitive issues concerning safety and/or efficacy of medicinal products. It is intended for hospital use only.
- **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-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

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

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

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

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).

Other substandard medicines (*n*= 560, 86%) were subjected to semi-urgent recalls (*n*= 536) or caution in use (*n*= 24). These were reported via the Health Product Recall type II (*n*= 288 medicines, 44%) and III (*n*= 245, 38%), PA (*n*= 8, 1%), HPC-NtoH (*n*= 9, 1%) and HPC-DHCPL (*n*= 7, 1%). Three medicines were recalled, but the corresponding type of Heath Product Recall was not given by Health Canada. The Majority of these drugs had stability, contamination and packaging defects (supplementary table 2).

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

Canada. Oversized tablets (i.e. tablets that exceed the weight requirement) were found in both drugs, raising the risk of the patients having 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.[17] 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 can be correlated 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] In January 2008, Health Canada introduced this policy as a response to increasing demand to update its policy on GMP, given that so many GMP guidelines and international agreements had been made since 1996. Subsequently, there has been a steady increase of incidents of substandard medicines from 2008 to 2013 (Figure 2). This policy illustrates the procedures that the Health Products and Food Branch (HPFB) follows to ensure that manufacturing sites, distributers and wholesalers are complying with GMP. It is conducted via inspections by the HPFB inspectorate with varying cycles, which depend on an approach that takes risk assessment into consideration, and a ranking scale of priority.[18] Similarly, it has been highlighted that most of the FDA recalls were related to FDA inspectors' visits in the USA.[19]

Manufacturing errors and investigation of the root cause

It is the responsibility of the manufacturers and marketing authorisation holders to recall their substandard products after consultation with Health Canada. The majority of these recalls were issued by the manufacturers or marketing authorisation holders using the Health Product Recall type I, II and III, which accounted for 95% of the total substandard medicines reported. Stability issues were mainly identified by the manufacturers during on-going stability testing. However, it is unknown whether these defects were identified by internal auditing systems of the manufacturers, by

intervention of the Health Canada inspection team or by reports from healthcare professionals.

Analysing pharmaceutical product recalls can be of great importance to identify the root causes of recalled medicines. The prompting of a drug recall can be regarded as a disastrous failure of the manufacturer's quality plan. Even with stringent quality measures, errors can occur.[20, 21] Thus, it is very important to identify the root cause of the defects to avoid similar episodes in the future. It has been highlighted in this review that stability failure and contamination issues were the defect types being reported most frequently. These issues affected several manufacturers on more than one occasion (supplementary table 4). This highlights the need for root cause investigations and appropriate measures to be implemented by manufacturers.

Falsified medicines

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

Comparison with the UK

Canada and the UK are two of the top pharmaceutical markets in the world, holding equal global pharmaceutical market share values of USD $21,877 and USD $21,635 billion, respectively.[22] They also use similar approaches in dealing with substandard medicines based on the expected risk. In the UK, the drug regulator uses four classes of drug alerts to communicate the risk of substandard medicines to Healthcare professionals.[6] A request to recall the affected batches is issued with the first three classes (class 1-3 drug alerts), comparable to the Health Product recall type I, II and III issued by Health Canada. A class 4 drug alert is issued by the UK drug regulator when a drug recall is not required, but caution is needed to deal with a substandard medicine. This type of communication is similar to the PA, HPC-NtoH

and HPC-DHCPL used by Health Canada. A class 1 drug recall (issued in the UK), and both the Health Product recall type I and PW (issued in Canada) are considered to be urgent communications. The rest of the documents in both countries are deemed as semi-urgent communications.[6, 14]

Out of the 280 substandard medicines found in the UK, 17 (6%) were subject to urgent communication.[7] The corresponding number in Canada was 89 (13%) out of 649. Overall, a larger number of substandard medicines were found in the Canadian supply chain (649 medicines) than in the UK (280 medicines).[7] The major contributor to this difference in our data was the number of medicines recalled due to stability problems (Figure 3), which were responsible for 50% of the difference. The differences in stability issues between Canada and the UK require further investigation.

Limitations

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

CONCLUSION

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. Regular GMP inspections on manufacturing sites were highlighted in this review as some of the most important tools that can improve detection of substandard medicines.

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.

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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
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

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 aoncentrates (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), nutrineal (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.

Quality of medicines in Canada: a retrospective review of risk 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 problem.[1-4] 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.

In Canada, Health products are regulated by Health Canada, which is the federal department responsible for the monitoring and regulating of medicines.[13] 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 also initiated to disseminate information regarding new safety issues of medicines or existing health risks to allow healthcare professionals and their patients to make well-informed decisions about their health.[14]

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

METHODS

Health Canada uses 13 risk communication documents, which can be issued for the public, healthcare professionals, and hospitals.[14] A preliminary search for these risk communication documents found that only five documents can be used by Health Canada to convey any defective health product issue in the Canadian official supply chain. These can be described as follows:

- **Public Warning (PW):** issued by Health Canada if the use of the drug can cause a severe adverse health consequence that may lead to death.
- **Public Advisory (PA):** issued by Health Canada if exposure to or the use of the drug can cause adverse health consequences, but is not life threatening or serious.
- **Healthcare Professional Communication - Notice to Hospitals (HPC-NtoH):** to inform the healthcare professional about time-sensitive issues concerning safety and/or efficacy of medicinal products. It is intended for hospital use only.
- **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-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

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

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

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

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).

Other substandard medicines (*n*= 560, 86%) were subjected to semi-urgent recalls (*n*= 536) or caution in use (*n*= 24). These were reported via the Health Product Recall type II (*n*= 288 medicines, 44%) and III (*n*= 245, 38%), PA (*n*= 8, 1%), HPC-NtoH (*n*= 9, 1%) and HPC-DHCPL (*n*= 7, 1%). Three medicines were recalled, but the corresponding type of Heath Product Recall was not given by Health Canada. The Majority of these drugs had stability, contamination and packaging defects (supplementary table 2).

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

Canada. Oversized tablets (i.e. tablets that exceed the weight requirement) were found in both drugs, raising the risk of the patients having 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.[17] 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 can be correlated 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] In January 2008, Health Canada introduced this policy as a response to increasing demand to update its policy on GMP, given that so many GMP guidelines and international agreements had been made since 1996. Subsequently, there has been a steady increase of incidents of substandard medicines from 2008 to 2013 (Figure 2). This policy illustrates the procedures that the Health Products and Food Branch (HPFB) follows to ensure that manufacturing sites, distributers and wholesalers are complying with GMP. It is conducted via inspections by the HPFB inspectorate with varying cycles, which depend on an approach that takes risk assessment into consideration, and a ranking scale of priority.[18] Similarly, it has been highlighted that most of the FDA recalls were related to FDA inspectors' visits in the USA.[19]

Manufacturing errors and investigation of the root cause

It is the responsibility of the manufacturers and marketing authorisation holders to recall their substandard products after consultation with Health Canada. The majority of these recalls were issued by the manufacturers or marketing authorisation holders using the Health Product Recall type I, II and III, which accounted for 95% of the total substandard medicines reported. Stability issues were mainly identified by the manufacturers during on-going stability testing. However, it is unknown whether these defects were identified by internal auditing systems of the manufacturers, by

intervention of the Health Canada inspection team or by reports from healthcare professionals.

Analysing pharmaceutical product recalls can be of great importance to identify the root causes of recalled medicines. The prompting of a drug recall can be regarded as a disastrous failure of the manufacturer's quality plan. Even with stringent quality measures, errors can occur.[20, 21] Thus, it is very important to identify the root cause of the defects to avoid similar episodes in the future. It has been highlighted in this review that stability failure and contamination issues were the defect types being reported most frequently. These issues affected several manufacturers on more than one occasion (supplementary table 4). This highlights the need for root cause investigations and appropriate measures to be implemented by manufacturers.

Falsified medicines

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

Comparison with the UK

Canada and the UK are two of the top pharmaceutical markets in the world, holding equal global pharmaceutical market share values of USD $21,877 and USD $21,635 billion, respectively.[22] They also use similar approaches in dealing with substandard medicines based on the expected risk. In the UK, the drug regulator uses four classes of drug alerts to communicate the risk of substandard medicines to Healthcare professionals.[6] A request to recall the affected batches is issued with the first three classes (class 1-3 drug alerts), comparable to the Health Product recall type I, II and III issued by Health Canada. A class 4 drug alert is issued by the UK drug regulator when a drug recall is not required, but caution is needed to deal with a substandard medicine. This type of communication is similar to the PA, HPC-NtoH

and HPC-DHCPL used by Health Canada. A class 1 drug recall (issued in the UK), and both the Health Product recall type I and PW (issued in Canada) are considered to be urgent communications. The rest of the documents in both countries are deemed as semi-urgent communications.[6, 14]

Out of the 280 substandard medicines found in the UK, 17 (6%) were subject to urgent communication.[7] The corresponding number in Canada was 89 (13%) out of 649. Overall, a larger number of substandard medicines were found in the Canadian supply chain (649 medicines) than in the UK (280 medicines).[7] The major contributor to this difference in our data was the number of medicines recalled due to stability problems (Figure 3), which were responsible for 50% of the difference. The differences in stability issues between Canada and the UK require further investigation.

Limitations

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

CONCLUSION

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. Regular GMP inspections on manufacturing sites were highlighted in this review as some of the most important tools that can improve detection of substandard medicines.

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.

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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
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

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 aoncentrates (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), nutrineal (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.

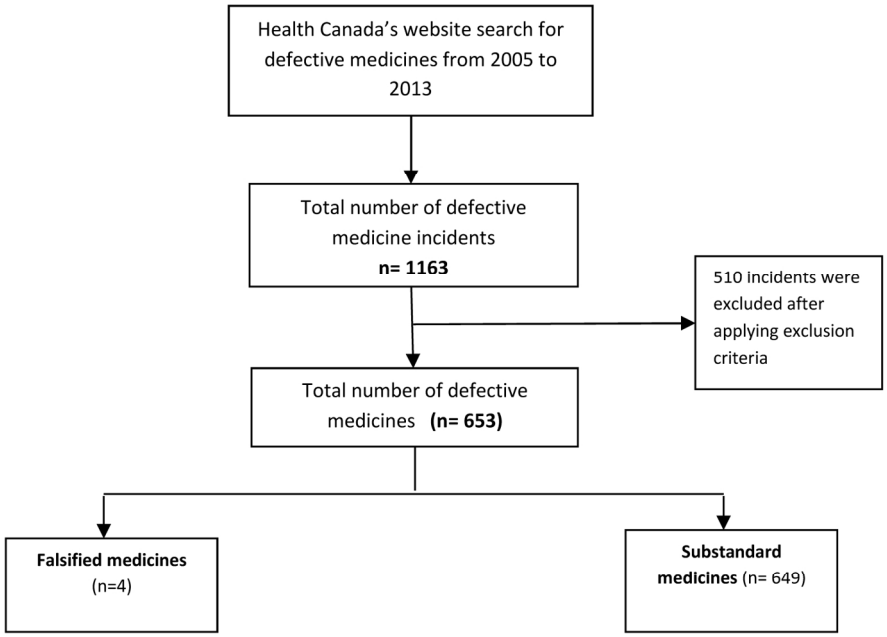

Figure 1: Flow diagram of search and resulting incidents.
148x103mm (300 x 300 DPI)

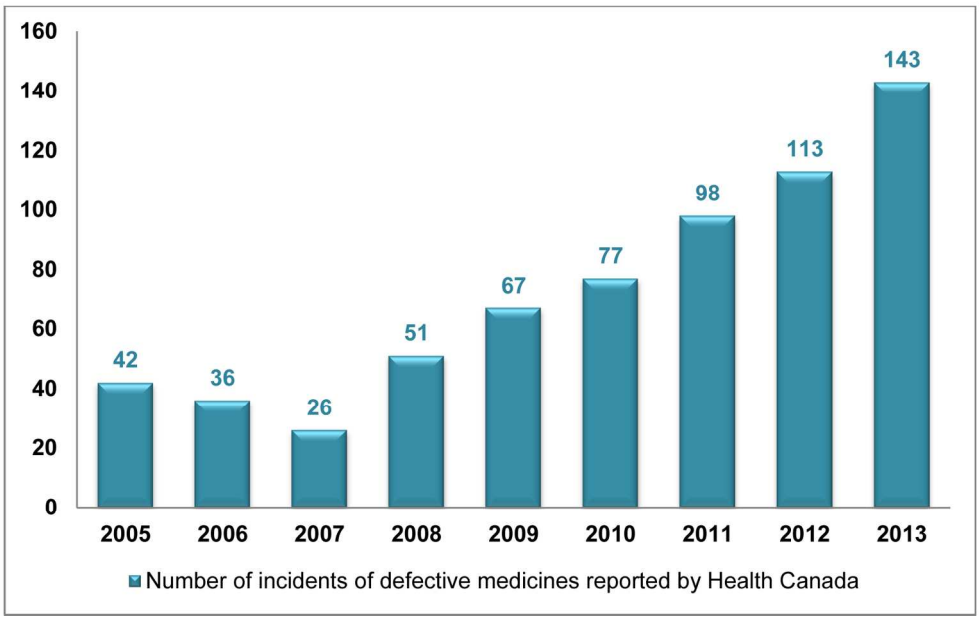

Figure 2: Number of incidents of defective medicines reported by Health Canada.
155x97mm (300 x 300 DPI)

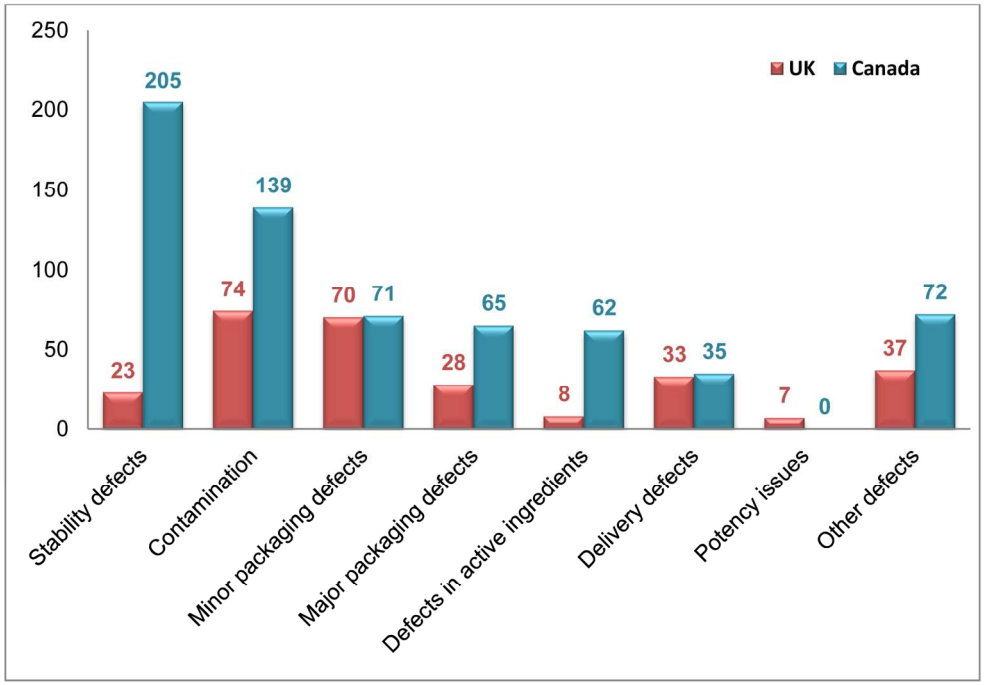

Figure 3: Comparison between Canada and the UK in the types of substandard medicines.
157x109mm (300 x 300 DPI)

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	65	10.0
			Psycholeptics	26	4.0
			Psychoanaleptics	18	2.8
			Anaesthetics	15	2.3
			Antiepileptics	13	2.0
			Anti-parkinson drugs	4	0.6
Alimentary tract and metabolism	90	13.9	Drugs for acid related disorders	25	3.9
			Vitamins	22	3.4
			Mineral supplements	16	2.5
			Laxatives	12	1.8
			Drugs used in diabetes	9	1.4
			Drugs for constipation	3	0.5
			Stomatological preparations	3	0.5
Cardiovascular System	83	12.8	Antihypertensives	50	7.7
			Lipid modifying agents	24	3.7
			Cardiac therapy	9	1.4
Anti-infectives for systemic use	65	10.0	Antibacterials for systemic use	38	5.9
			Antimycotics for systemic use	8	1.2
			Immune sera and immunoglobulins	8	1.2
			Vaccines	6	0.9
			Antivirals for systemic use	5	0.8
Blood and blood forming organs	63	9.7	Blood substitutes and perfusion solutions	30	4.6
			Antithrombotic agents	19	2.9
			Antianemic preparations	14	2.2
Dermatologicals	46	7.1	Corticosteroids, dermatological preparations	18	2.8
			Other dermatological preparations	14	2.2
			Anti-acne preparations	9	1.4
			Antifungals for dermatological use	5	0.8
Respiratory system	31	4.8	Antihistamines for systemic use	11	1.7
			Cough and cold preparations	11	1.7
			Drugs for obstructive airway diseases	7	1.1
			Nasal preparations	2	0.3
Genito-urinary system and sex hormones	29	4.5	Sex hormones and modulators of the genital system	22	3.4
			Urologicals	5	0.8
			Gynecological antiinfectives and antiseptics	2	0.3
Antineoplastic and immunomodulating agents	28	4.3	Antineoplastic agents	18	2.8
			Immunosuppressants	4	0.6
			Immunostimulants	4	0.6
			Endocrine therapy	2	0.3
Various	26	4.0	Diagnostic radiopharmaceuticals	20	3.1
			All other therapeutic products	4	0.6
			Contrast media	2	0.3
Sensory organs	21	3.2	Ophthalmologicals	20	3.1
			Otologicals	1	0.2
Musculo-skeletal system	18	2.8	Antiinflammatory and antirheumatic products	11	1.7
			Drugs for treatment of bone diseases	6	0.9
			Muscle relaxants	1	0.2
Systemic hormonal preparations, excluding sex hormones and insulins	8	1.2	Pituitary and hypothalamic hormones and analogues	3	0.5
			Pancreatic hormones	3	0.5
			Pituitary and hypothalamic hormones and analogues	2	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.

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

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Quality of medicines in Canada: a retrospective review of risk 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 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 problem.[1-4] 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

defective medicines has never been explored in this setting and because of the level of data available in the public domain.

In Canada, Health products are regulated by Health Canada, which is the federal department responsible for the monitoring and regulating of medicines.[13] 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 also initiated to disseminate information regarding new safety issues of medicines or existing health risks to allow healthcare professionals and their patients to make well-informed decisions about their health.[14]

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

METHODS

Health Canada uses 13 risk communication documents, which can be issued for the public, healthcare professionals, and hospitals.[14] A preliminary search for these risk communication documents found that only five documents can be used by Health Canada to convey any defective health product issue in the Canadian official supply chain. These can be described as follows:

- **Public Warning (PW):** issued by Health Canada if the use of the drug can cause a severe adverse health consequence that may lead to death.
- **Public Advisory (PA):** issued by Health Canada if exposure to or the use of the drug can cause adverse health consequences, but is not life threatening or serious.
- **Healthcare Professional Communication - Notice to Hospitals (HPC-NtoH):** to inform the healthcare professional about time-sensitive issues concerning safety and/or efficacy of medicinal products. It is intended for hospital use only.

- **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-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 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.

All relevant information regarding defective health products was compiled and exclusion criteria were as follows: veterinary medicines; medicines lacking efficacy or acquiring general safety issues; herbal and probiotic products; dietary and cosmetic products; and other natural heath product recalled for regulatory reason (i.e., those do not have a valid marketing authorisation). The following data were extracted from the risk communication documents: name, strength, and dosage form; year of the document; nature of the defect; type of drug recall (in the case of Health Product Recalls); and action to be taken by healthcare professionals or the public regarding the defective medicine. In the case of Health Product Recalls and PW, the action is to remove the defective medicine from the dispensary shelves and contact the manufacturer for return. Whereas, with other risk communication documents where there is no recall required, healthcare professionals and the public are given advice on how to deal with defective medicines and to alert the public to be aware of expected risks. Two types of drugs can be distinguished from risk communication documents; substandard drugs and falsified drugs. The decision on which incident was falsified or substandard is that published by Health Canada.

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

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

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 a p value <0.05. The comparison was conducted to investigate if there are certain types of quality defects (e.g., stability or packaging issues) that were more likely to be reported with distributors, as this may indicate non-compliance with Good Distribution Practices.

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).

Other substandard medicines (*n*= 560, 86%) were subjected to semi-urgent recalls (*n*= 536) or caution in use (*n*= 24). These were reported via the Health Product Recall type II (*n*= 288 medicines, 44%) and III (*n*= 245, 38%), PA (*n*= 8, 1%), HPC-NtoH (*n*= 9, 1%) and HPC-DHCPL (*n*= 7, 1%). Three medicines were recalled, but the corresponding type of Heath Product Recall was not given by Health Canada. The majority of these drugs had stability, contamination and packaging defects (supplementary table 2).

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

contaminated. Products of Sandoz Canada Inc. had a problem with the active ingredient; the concentration 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 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

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

Manufacturing errors and investigation of the root cause

It is the responsibility of the manufacturers and marketing authorisation holders to recall their substandard products after consultation with Health Canada. The majority of these recalls were issued by the manufacturers or marketing authorisation holders using the Health Product Recall type I, II and III, which accounted for 95% of the total substandard medicines reported. Stability issues were mainly identified by the manufacturers during on-going stability testing. However, it is unknown whether these defects were identified by internal auditing systems of the manufacturers, by intervention of the Health Canada inspection team or by reports from healthcare professionals.

Analysing pharmaceutical product recalls can be of great importance to identify the root causes of recalled medicines. The prompting of a drug recall can be regarded as a disastrous failure of the manufacturer's quality plan. Even with stringent quality measures, errors can occur.[21, 22] Thus, it is very important to identify the root cause of the defects to avoid similar episodes in the future. The root cause for a defect is required to be submitted to Health Canada, as soon as it is identified, along with other information relating to the quantity and depth of the distribution of the affected medicine. It is the responsibility of Health Canada to monitor the overall procedure and assess the root cause for this problem and, if required, to conduct an inspection to verify that a corrective action is implemented.[23, 24] It has been highlighted in this review

that stability failure and contamination issues were the defect types being reported most frequently. These issues affected several manufacturers on more than one occasion (supplementary table 4). This highlights the need for root cause investigations and appropriate measures to be implemented by manufacturers as well as effective monitoring by Health Canada.

Falsified medicines

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

Comparison with the UK

Despite the fact that Canada and the UK represent 2% (for each) of the global pharmaceutical market volume, they are two of the top markets by value of marketed medicines. Canada and the UK hold equal global pharmaceutical market share values of USD $21,877 and USD $21,635 billion, respectively.[25] They also use similar approaches in dealing with substandard medicines based on the expected risk. In the UK, the drug regulator uses four classes of drug alerts to communicate the risk of substandard medicines to Healthcare professionals.[6] A request to recall the affected batches is issued with the first three classes (class 1-3 drug alerts), comparable to the Health Product recall type I, II and III issued by Health Canada. A class 4 drug alert is issued by the UK drug regulator when a drug recall is not required, but caution is needed to deal with a substandard medicine. This type of communication is similar to the PA, HPC-NtoH and HPC-DHCPL used by Health Canada. A class 1 drug recall (issued in the UK), and both the Health Product recall type I and PW (issued in Canada) are considered to be urgent communications. The rest of the documents in both countries are deemed as semi-urgent communications.[6, 14]

Out of the 280 substandard medicines found in the UK, 17 (6%) were subject to urgent communication.[7] The corresponding number in Canada was 89 (14%) out of 649. Overall, a larger number of substandard medicines were found in the Canadian supply chain (649 medicines) than in the UK (280 medicines).[7] It is also important to mention that the UK study was conducted over a longer period (i.e., 11 years) than the one on Canada (i.e., 9 years). Therefore, the difference in the number of substandard medicines may be even larger than it appears. The major contributor to this difference in our data was the number of medicines recalled due to stability problems (Figure 3), which were responsible for 50% of the difference. The differences in stability issues between Canada and the UK require further investigation.

Limitations

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

CONCLUSION

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. Regular GMP inspections on manufacturing sites were highlighted in this review as some of the most important tools that can improve detection of substandard medicines.

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.

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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
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

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 aoncentrates (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), nutrineal (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.

Quality of medicines in Canada: a retrospective review of risk 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 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 problem.[1-4] 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

defective medicines has never been explored in this setting and because of the level of data available in the public domain.

In Canada, Health products are regulated by Health Canada, which is the federal department responsible for the monitoring and regulating of medicines.[13] 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 also initiated to disseminate information regarding new safety issues of medicines or existing health risks to allow healthcare professionals and their patients to make well-informed decisions about their health.[14]

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

METHODS

Health Canada uses 13 risk communication documents, which can be issued for the public, healthcare professionals, and hospitals.[14] A preliminary search for these risk communication documents found that only five documents can be used by Health Canada to convey any defective health product issue in the Canadian official supply chain. These can be described as follows:

- **Public Warning (PW):** issued by Health Canada if the use of the drug can cause a severe adverse health consequence that may lead to death.
- **Public Advisory (PA):** issued by Health Canada if exposure to or the use of the drug can cause adverse health consequences, but is not life threatening or serious.
- **Healthcare Professional Communication - Notice to Hospitals (HPC-NtoH):** to inform the healthcare professional about time-sensitive issues concerning safety and/or efficacy of medicinal products. It is intended for hospital use only.

- **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-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 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.

All relevant information regarding defective health products was compiled and exclusion criteria were as follows: veterinary medicines; medicines lacking efficacy or acquiring general safety issues; herbal and probiotic products; dietary and cosmetic products; and other natural heath product recalled for regulatory reason (i.e., those do not have a valid marketing authorisation). The following data were extracted from the risk communication documents: name, strength, and dosage form; year of the document; nature of the defect; type of drug recall (in the case of Health Product Recalls); and action to be taken by healthcare professionals or the public regarding the defective medicine. In the case of Health Product Recalls and PW, the action is to remove the defective medicine from the dispensary shelves and contact the manufacturer for return. Whereas, with other risk communication documents where there is no recall required, healthcare professionals and the public are given advice on how to deal with defective medicines and to alert the public to be aware of expected risks. Two types of drugs can be distinguished from risk communication documents; substandard drugs and falsified drugs. The decision on which incident was falsified or substandard is that published by Health Canada.

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

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

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 a p value <0.05. The comparison was conducted to investigate if there are certain types of quality defects (e.g., stability or packaging issues) that were more likely to be reported with distributors, as this may indicate non-compliance with Good Distribution Practices.

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).

Other substandard medicines (*n*= 560, 86%) were subjected to semi-urgent recalls (*n*= 536) or caution in use (*n*= 24). These were reported via the Health Product Recall type II (*n*= 288 medicines, 44%) and III (*n*= 245, 38%), PA (*n*= 8, 1%), HPC-NtoH (*n*= 9, 1%) and HPC-DHCPL (*n*= 7, 1%). Three medicines were recalled, but the corresponding type of Heath Product Recall was not given by Health Canada. The majority of these drugs had stability, contamination and packaging defects (supplementary table 2).

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

contaminated. Products of Sandoz Canada Inc. had a problem with the active ingredient; the concentration 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 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

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

Manufacturing errors and investigation of the root cause

It is the responsibility of the manufacturers and marketing authorisation holders to recall their substandard products after consultation with Health Canada. The majority of these recalls were issued by the manufacturers or marketing authorisation holders using the Health Product Recall type I, II and III, which accounted for 95% of the total substandard medicines reported. Stability issues were mainly identified by the manufacturers during on-going stability testing. However, it is unknown whether these defects were identified by internal auditing systems of the manufacturers, by intervention of the Health Canada inspection team or by reports from healthcare professionals.

Analysing pharmaceutical product recalls can be of great importance to identify the root causes of recalled medicines. The prompting of a drug recall can be regarded as a disastrous failure of the manufacturer's quality plan. Even with stringent quality measures, errors can occur.[21, 22] Thus, it is very important to identify the root cause of the defects to avoid similar episodes in the future. The root cause for a defect is required to be submitted to Health Canada, as soon as it is identified, along with other information relating to the quantity and depth of the distribution of the affected medicine. It is the responsibility of Health Canada to monitor the overall procedure and assess the root cause for this problem and, if required, to conduct an inspection to verify that a corrective action is implemented.[23, 24] It has been highlighted in this review

that stability failure and contamination issues were the defect types being reported most frequently. These issues affected several manufacturers on more than one occasion (supplementary table 4). This highlights the need for root cause investigations and appropriate measures to be implemented by manufacturers as well as effective monitoring by Health Canada.

Falsified medicines

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

Comparison with the UK

Despite the fact that Canada and the UK represent 2% (for each) of the global pharmaceutical market volume, they are two of the top markets by value of marketed medicines. Canada and the UK hold equal global pharmaceutical market share values of USD $21,877 and USD $21,635 billion, respectively.[25] They also use similar approaches in dealing with substandard medicines based on the expected risk. In the UK, the drug regulator uses four classes of drug alerts to communicate the risk of substandard medicines to Healthcare professionals.[6] A request to recall the affected batches is issued with the first three classes (class 1-3 drug alerts), comparable to the Health Product recall type I, II and III issued by Health Canada. A class 4 drug alert is issued by the UK drug regulator when a drug recall is not required, but caution is needed to deal with a substandard medicine. This type of communication is similar to the PA, HPC-NtoH and HPC-DHCPL used by Health Canada. A class 1 drug recall (issued in the UK), and both the Health Product recall type I and PW (issued in Canada) are considered to be urgent communications. The rest of the documents in both countries are deemed as semi-urgent communications.[6, 14]

Out of the 280 substandard medicines found in the UK, 17 (6%) were subject to urgent communication.[7] The corresponding number in Canada was 89 (14%) out of 649. Overall, a larger number of substandard medicines were found in the Canadian supply chain (649 medicines) than in the UK (280 medicines).[7] It is also important to mention that the UK study was conducted over a longer period (i.e., 11 years) than the one on Canada (i.e., 9 years). Therefore, the difference in the number of substandard medicines may be even larger than it appears. The major contributor to this difference in our data was the number of medicines recalled due to stability problems (Figure 3), which were responsible for 50% of the difference. The differences in stability issues between Canada and the UK require further investigation.

Limitations

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

CONCLUSION

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. Regular GMP inspections on manufacturing sites were highlighted in this review as some of the most important tools that can improve detection of substandard medicines.

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.

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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
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

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 aoncentrates (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), nutrineal (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.

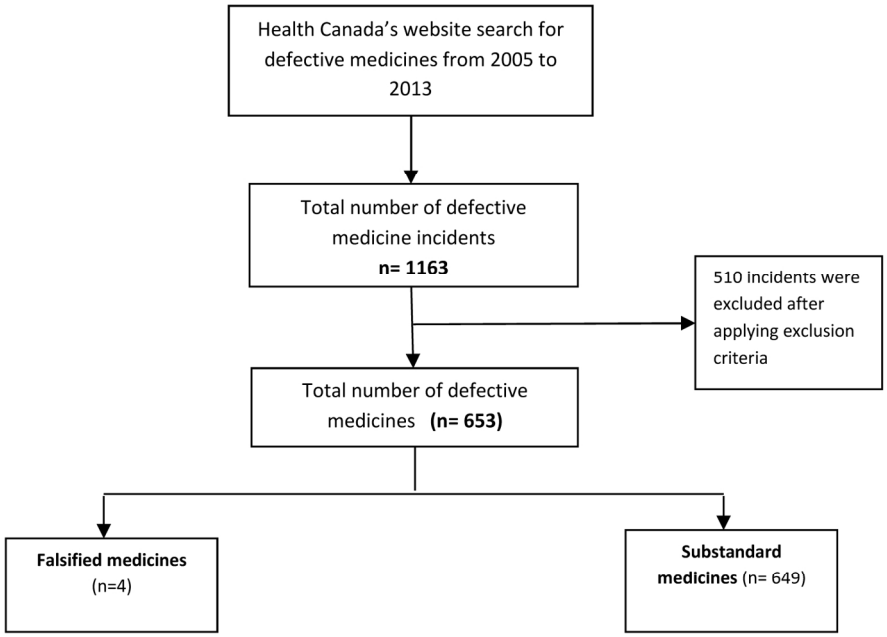

Figure 1: Flow diagram of search and resulting incidents.
148x103mm (300 x 300 DPI)

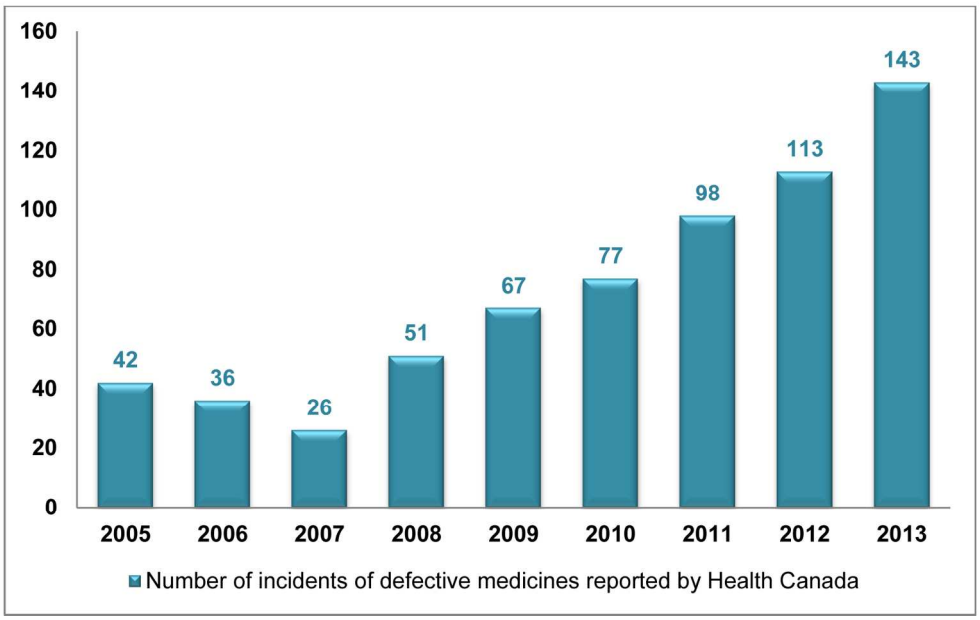

Figure 2: Number of incidents of defective medicines reported by Health Canada.
155x97mm (300 x 300 DPI)

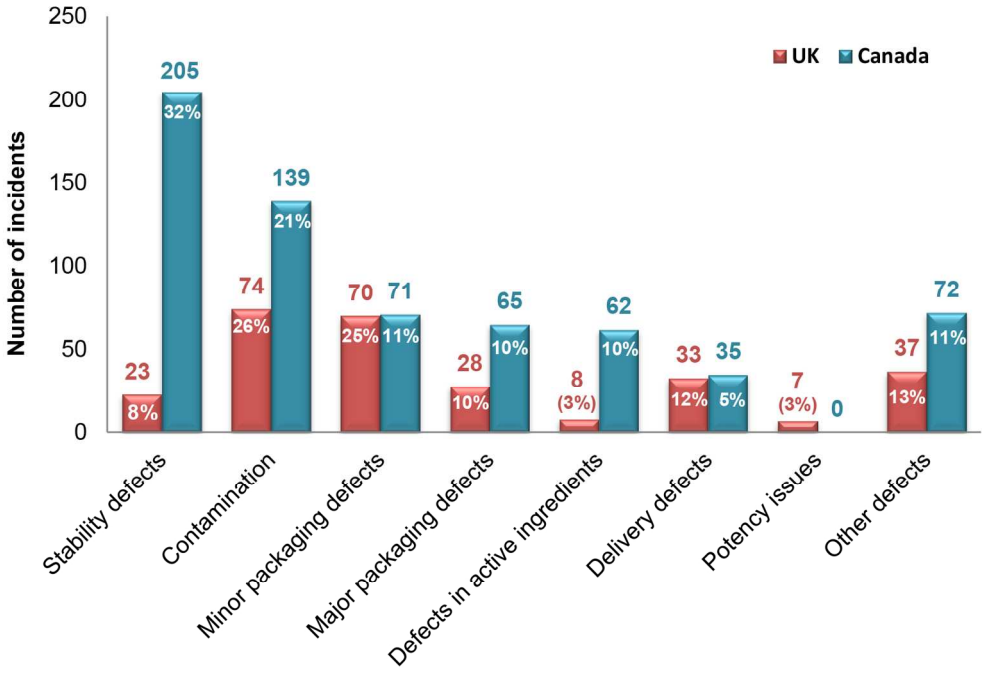

Figure 3: Comparison between Canada and the UK in the types of substandard medicines reported. Percentages are given based on the total number of incidents reported in each country.
151x103mm (300 x 300 DPI)

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	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.