



Original article

Comparison of the safety information on drug labels in three developed countries: The USA, UK and Canada

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ABSTRACT

The safety information on drug labels of a company marketing the same drugs in different countries is sometimes different. The aim of the present study is to understand the differences in the volume and content of safety information on the drug labels from the same manufacturers in three developed countries: the United States of America (USA), the United Kingdom (UK) and Canada. This study involved the calculation of the proportion of total safety information (PSI) and of contraindications (PCI) in comparison to all information on the label and the percentage of boxed warnings (PBW) among the 100 labels studied from each country. The PSI on the labels of different countries is different with USA labels bearing lesser value PSI and UK labels bearing higher value PSI. The qualitative information provided on these drug labels from each country in 'contraindications' sections, 'boxed/serious warnings' and 'overdosage' sections presented differences in the information provided on most of the labels. We have found distinct differences between the safety information available on drug labels in terms of volume and content. We conclude that the safety information for the same products should be standardised across all countries. © 2017 The Authors. Production and hosting by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Drug labels are the essential means of communication of important information on drug safety to healthcare professionals and patients (Davis et al., 2006). These labels are the primary source of information from manufacturers to healthcare professionals (Duke et al., 2011). Drug labels are prepared by the manufacturers and are reviewed by the Food and Drug Administration (FDA) or a similar body in a particular country (Cooper, 1986). Guidelines for the structure and content of drug labels are generally given by the regulatory authorities of the respective countries. In the United States of America (USA), the FDA issues guidance for requirements

on content and format of labelling. In United Kingdom (UK), Summaries of Product Characteristics (SPCs) are checked and approved by the Medicines and Healthcare Products Regulatory Agency (MHRA), and in Canada, Health Canada looks after the information on drug labels (DailyMed, 2016; Electronics Medical Compendium, 2016; Health Canada, 2016). Generally, drug labels contain useful information about the therapeutic indications, dosing, drug interactions, adverse drug effects and the drug's toxicity details (Requirements on Content and Format of Labelling for Human Prescription Drug and Biological Products. Final Rule, 2006). The labels are available on the websites of the regulatory authorities and are updated regularly in the light of important new information on the specific drug (Raymond, 2000). Many labels contain comprehensive lists of adverse events. However, exhaustive lists of adverse events result in the poor readability of the labels, which consequently may result in overlooking serious risks and warnings (Duke et al., 2011). Regulatory authorities continuously monitor drug labels to improve the readability and understandability of the labels and as well as ensure any new drug safety information is listed (Blank, 2015; King et al., 2016; Kircik et al., 2016). Studies have also focused on improving the readability of the labels (Abedtash and Duke, 2015).

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We would expect that the information on drug labels in different countries for the same drug would be similar as the regulatory authorities evaluate the same scientific data (Shimazawa and Ikeda, 2013a). This expectation is high, particularly when the drug is supplied by the same manufacturer in different countries. In this study, we assessed the safety information on the labels supplied by the same company in different countries. The aim of the present study is to investigate any differences in safety information in developed countries and to provide an evidence base for better drug safety communication.

2. Methods

2.1. Data sources

This study was a cross-sectional study conducted in the period between January and March 2016. The present study included drugs approved in the USA, the UK and Canada. The drug labels were identified from the DailyMed, electronics Medical Compendium (eMC) and Health Canada for the USA, the UK and Canada, respectively (DailyMed, 2016; Electronics Medical Compendium, 2016; Health Canada, 2016). Structured product labels, summaries of product characteristics and product monographs were used from the above said websites in the USA, the UK and Canada, respectively. From these labels, we randomly identified labels that are prepared by the same company in all three countries by manual search. Three hundred such labels were used in our study, 100 from each country. These drug labels were also analysed qualitatively for the information provided in the 'contraindications' sections, 'boxed/serious warnings' and 'overdose' sections. Differences in information within these sections were identified manually and listed in Tables.

2.2. Variable definitions, evaluation and analysis

We performed a direct comparison of the proportion of all information given to safety information (PSI), and contraindications (PCI) in the three countries. The PSI was calculated by dividing the total number of safety words with the total number of label words. The PCI was calculated by dividing the number of words on contraindications to the total number of words on the label. Similarly, the percentage of boxed warnings (PBW, in the USA and Canada) was calculated by dividing the number of labels with boxed warnings and the total number of labels. The total number of safety words was calculated based on the sections listed in Table 1 from each country. Boxed warnings or serious warnings were identified by manual search on USA drug labels or Canadian drug labels, which we included in calculating safety words for that particular country. In regard to the UK, there are no warnings given in a special box for any drug on the label from the drugs we

screened in our study. However, on some labels there is a box on serious adverse effects; for example, on the label of thalidomide, we can find a boxed warning for teratogenic effects (Thalidomide Drug Label in UK, 2016). The label information was analysed after grouping the drugs according to Anatomical Therapeutic Chemical (ATC) classification codes (Table 2).

2.3. Qualitative comparison of the product label information

There is a possibility that the volume of text is different, but the information conveyed is the same. To understand the differences in the information provided across the three countries, the actual information that is illustrated in the contraindications sections, serious/boxed warnings and overdosage sections was read, and information that was different was identified and tabulated.

2.4. Statistical analysis

Descriptive statistics were performed on the data obtained. Data were presented as the mean and standard deviation (SD). One way analysis of variance (One way ANOVA) was performed to find out the differences between groups followed by Scheffe's post hoc test to determine which means were different with a level of significance set at $p < 0.05$. Data were analysed using Statistical Analysis Software (SAS version 9.3).

3. Results and discussion

A total of 100 drug labels in each country were counted for the total number of words on the label. The total number of label words on the Canadian labels (14843 [7018] (Average [standard deviation])) was higher than the number of USA (10724 [6406]) and UK (5637 [3379]) label words with a p value < 0.05 . The total number of safety words was also higher on Canadian labels (6235 [3486]) when compared to the USA (3873 [2616]) and the UK (2757 [1674]) label safety words with a p value < 0.05 . The number of words on the label indicating contraindications was higher in Canada (83 [73]) than for the UK (49 [47]) with a p value < 0.05 . Overall, the number of words on the label, safety information words and contraindication words were higher in Canada.

We have noticed differences in the amount of information provided on the drug labels although the labels were prepared by the same manufacturers in the USA, the UK and Canada (Online only Tables S1–S6). The USA and Canadian labels contained almost double the volume of information contained in the UK labels. Although the regulatory authorities reviewed the labels by the same manufacturer, the information on the USA and Canadian labels is more voluminous most likely due to the guidelines set by these authorities for the preparation of drug labels (Best

Table 1
Drug label information for analysis.

Categories for analysis	Drug label sections		
	USA	UK	Canada
Safety information	Boxed warnings 4. Contraindications 5. Warnings and precautions 6. Adverse reactions 7. Drug interactions 8. Use in specific populations 10. Over dosage 13. Non clinical toxicology	4.3 Contraindications 4.4 Special warnings and precautions 4.5 Interaction with other medicinal products 4.6 Pregnancy and lactation 4.7 Effects on ability to drive and use machines 4.8 Undesirable effects 4.9 Overdose 5.3 Preclinical safety data	Serious warnings Contraindications Warnings and precautions Adverse reactions Drug interactions Over dosage Toxicology
Contraindications	4. Contraindications	4.3 Contraindications	Contraindications
Serious warnings	Boxed warnings	Not applicable	Serious warnings and precautions

Table 2
Drug labels stratified by Anatomical Therapeutic Chemical (ATC) classification.

ATC code	Contents	Number of labels
A	Alimentary tract and metabolism	7
B	Blood and blood-forming organs	4
C	Cardiovascular system	7
D	Dermatologicals	7
G	Genitourinary system and sex hormones	5
H	Systemic hormonal preparations, excluding sex hormones	4
J	General anti-infectives for systemic use	12
L	Antineoplastic and immunomodulating agents	21
M	Musculo-skeletal system	4
N	Nervous system	16
R	Respiratory system	3
S	Sensory organs	8
V	Various	2

Practice Guidance on the Labelling, 2016; Guidance Document, 2016, Labeling, 2016).

Different laws in different countries can affect regulatory decisions (Shimazawa and Ikeda, 2013a). Differences in doses, indications and safety exist among regions (Arnold et al., 2010; Malinowski et al., 2008). These differences can be due to biological and non-biological factors (Shimazawa and Ikeda, 2013a). Biological factors, such as racial differences, can affect the pharmacokinetics and thus the dose and dosage regimen on the labels. Non-biological factors, such as regulatory requirements, healthcare systems and the general public's perception, can also affect the information provided on the drug labels. For example, boxed warnings were included in the USA and Canadian labels but not included in most of the UK drug labels. On some of the UK drug labels, such as on thalidomide, a box was drawn around the important warning in the section '4.4 Special warnings and precautions for use'; however, in our study, we found no such boxed warnings for the drugs identified. Boxed warnings are used to highlight adverse events that may result in death or serious injury with the use of a particular drug (Beach et al., 1998; Cook et al., 2009).

3.1. Proportion of total safety information

Table 3 shows the proportion of total safety information on drug labels in three countries. Mean PSI on the total labels was different among the countries, with the UK showing the highest percentage and the USA showing the lowest percentage. Drug labels in the USA with codes A (30 [9]), D (34 [9]) and G (34 [7]) have less information than on UK labels, which had percentages of 46 [12], 50 [10] and 47 [6] for the same codes, respectively. Code J drug labels contained less information on USA (30 [4]) labels than on

UK (47 [11]) and Canadian (39 [8]) labels (Table 3). Table S1 shows a direct comparison of PSI across the same drug in each therapeutic area among different countries.

Mean PSI was found to be higher on UK labels than in the other two countries. In a previous study conducted on the labels of new molecular entities between the USA, the UK and Japan, it was found that the mean PSI was similar, but there were differences in labels with ATC code N (Shimazawa and Ikeda, 2013a). However, in our study, we found that there are significant differences among the mean PSI of all three countries. The studies to establish safety and adverse events, which are being conducted now, have not been conducted previously as these generic drug products were approved long ago and were found to be safe with the long years of usage since their approvals. Another reason could be the rigorous post-marketing surveillance and rigorous clinical trials of the new drugs when compared to the older generic drugs.

3.2. Proportion of contraindications

The mean PCI was larger in the UK (1.2% [1.3]) for all 100 drugs than in the USA (0.7% [1.2]) and Canada (0.7% [0.7]). On 5 labels, no contraindications section was present on the USA drug labels (PCI 0%); however, contraindications were listed for these drugs on UK and Canadian drug labels (Table 4). Table S2 shows a direct comparison of PCI across the same drug in each therapeutic area.

The number of words on contraindications suggested that the UK labels contained fewer words when compared to the Canadian labels. However, when this number is calculated as PCI, UK labels depicted a higher PCI value than the USA and Canadian drug labels. This result could be attributed to the vast information available on the USA and Canadian labels when compared to UK labels. There is a difference in reporting the contraindications on the labels from country to country.

3.3. Labels with a boxed/serious warning

Among all the labels screened, 37 labels from the USA contained boxed warnings and 47 labels from Canada possessed serious warnings that are similar to the boxed warnings in the USA (Tables 5 and S3). Drugs belonging to classes R and S have no boxed warnings on USA labels and no serious warnings on Canadian labels, which does not mean that all the drugs belonging to classes R and S do not have boxed warnings. It means that in only our study, we were unable to find any drug in these categories with boxed warnings. Among classes D, G and H, there are no boxed warnings on USA labels, but serious warnings were present on Canadian labels. The PBW in classes B, C and V is higher on USA labels (50%, 86% and 100%, respectively) when compared to Canadian labels (25%, 71% and 50%, respectively). Similar percentages were

Table 3
proportion of total safety information on the label.

ATC code	A (n = 7)	B (n = 4)	C (n = 7)	D (n = 7)	G (n = 5)	H (n = 4)	J (n = 12)	L (n = 21)	M (n = 4)	N (n = 16)	R (n = 3)	S (n = 8)	V (n = 2)	All (n = 100)
USA	30 [9] [#]	30 [5]	40 [5]	34 [9] [#]	34 [7] [#]	31 [14]	30 [4] [@]	40 [9]	42 [9]	41 [12]	31 [9]	44 [8]	37 [5]	37 [10]
UK	46 [12]	47 [7]	48 [2]	50 [10]	47 [6]	49 [3]	47 [11]	49 [12] [†]	48 [7]	56 [10]	45 [7]	54 [8]	45 [11]	50 [10] [*]
Canada	38 [12]	44 [18]	50 [11]	44 [10]	42 [9]	35 [9]	39 [8]	40 [10]	47 [12]	48 [9]	36 [3]	37 [11]	31 [4]	42 [11]
p value	0.04	0.15	0.04 [§]	0.02	0.02	0.06	<0.001	0.01	0.67	<0.001 [§]	0.11	<0.01 [§]	0.32	<0.001

Abbreviations: ATC, Anatomical Therapeutic Chemical; A, alimentary tract and metabolism; B, blood and blood-forming organs; C, cardiovascular system; D, dermatologicals; G, genitourinary system and sex hormones; H, systemic hormonal preparations, excluding sex hormones; J, general anti-infectives for systemic use; L, antineoplastic and immunomodulating agents; M, musculo-skeletal system; N, nervous system; R, respiratory system; S, sensory organs; and V, various. Values are means % [standard deviation].

[#] Smaller than UK.

[@] Smaller than UK and Canada.

[†] Larger than US and Canada.

[§] Analysis of variance suggests a p value < 0.05, but Scheffe's post hoc test doesn't show any significant difference between the means.

Table 4
Proportion of contraindications to all information on the label.

ATC code	A (n = 7)	B (n = 4)	C (n = 7)	D (n = 7)	G (n = 5)	H (n = 4)	J (n = 12)	L (n = 21)	M (n = 4)	N (n = 16)	R (n = 3)	S (n = 8)	V (n = 2)	All (n = 100)
USA	0.4 [0.5]	0.9 [0.6]	0.7 [0.6]	2.2 [4.0]	1.5 [1.1]	0.8 [0.6]	0.4 [0.4]	0.5 [0.7]	0.7 [0.4]	0.5 [0.6]	0.4 [0.3]	1.0 [0.6]	0.4 [0.3]	0.7 [1.2]
UK	1.1 [1.6]	2.5 [3.2]	1.7 [0.9]	1.3 [0.9]	3.0 [2.2]	1.8 [1.5]	0.7 [0.5]	0.7 [0.7]	1.0 [1.0]	1.1 [1.4]	0.5 [0.1]	1.2 [0.6]	0.5 [0.2]	1.2 [1.3]
Canada	0.5 [0.4]	1.4 [1.5]	1.6 [0.7]	0.6 [0.2]	1.2 [1.7]	0.8 [0.6]	0.4 [0.4]	0.4 [0.4]	0.7 [0.6]	0.6 [0.6]	0.3 [0.2]	0.7 [0.5]	0.8 [0.1]	0.7 [0.7]
p value	0.40	0.57	0.04 [§]	0.46	0.24	0.29	0.25	0.46	0.82	0.14	0.64	0.31	0.34	<0.01

Abbreviations: ATC, Anatomical Therapeutic Chemical; A, alimentary tract and metabolism; B, blood and blood-forming organs; C, cardiovascular system; D, dermatologicals; G, genitourinary system and sex hormones; H, systemic hormonal preparations, excluding sex hormones; J, general anti-infectives for systemic use; L, antineoplastic and immunomodulating agents; M, musculo-skeletal system; N, nervous system; R, respiratory system; S, sensory organs; and V, various. Values are means % [standard deviation].

[†] Larger than US and Canada.

[§] Analysis of variance suggests a p value < 0.05, but Scheffe's post hoc test doesn't show any significant difference between the means.

Table 5
Proportion of the number of labels with a boxed warning to that of all labels.

ATC code	A (n = 7)	B (n = 4)	C (n = 7)	D (n = 7)	G (n = 5)	H (n = 4)	J (n = 12)	L (n = 21)	M (n = 4)	N (n = 16)	R (n = 3)	S (n = 8)	V (n = 2)	All (n = 100)
USA	29 (2)	50 (2)	86 (6)	0	0	0	42 (5)	52 (11)	50 (2)	44 (7)	0	0	100 (2)	37 (37)
Canada	29 (2)	25 (1)	71 (5)	29 (2)	40 (2)	50 (2)	42 (5)	81 (17)	50 (2)	50 (8)	0	0	50 (1)	47 (47)
USA+/ Canada [†]	29 (2)	0	71 (5)	0	0	0	42 (5)	48 (10)	50 (2)	38 (6)	0	0	50 (1)	31 (31)
USA+/ Canada ⁻	14 (1)	50 (2)	14 (1)	0	0	0	0	5 (1)	0	6 (1)	0	0	50 (1)	7 (7)
USA-/ Canada [†]	14 (1)	25 (1)	0	29 (2)	40 (2)	50 (2)	0	33 (7)	0	13 (2)	0	0	0	17 (17)
USA-/ Canada ⁻	57 (4)	25 (1)	14 (1)	71 (5)	60 (3)	50 (2)	58 (7)	14 (3)	50 (2)	44 (7)	100 (3)	100 (8)	0	35 (35)
Concordance [*]	86 (6)	25 (1)	86 (6)	71 (5)	60 (3)	50 (2)	100 (12)	62 (13)	100 (4)	81 (13)	100 (3)	100 (8)	50 (1)	66 (66)

Abbreviations: ATC, Anatomical Therapeutic Chemical; A, alimentary tract and metabolism; B, blood and blood-forming organs; C, cardiovascular system; D, dermatologicals; G, genitourinary system and sex hormones; H, systemic hormonal preparations, excluding sex hormones; J, general anti-infectives for systemic use; L, antineoplastic and immunomodulating agents; M, musculo-skeletal system; N, nervous system; R, respiratory system; S, sensory organs; and V, various. Values are % (number).

[†] Represents labels with boxed/serious warning.

⁻ Represents labels without boxed/serious warning.

^{*} Concordance represents the sum of labels with a boxed warning both in the US and in Canada and those without a boxed warning in the US or in Canada.

observed in codes A (29%), J (42%) and M (50%) for both countries. Among different classes, 66% concordance was observed between USA and Canadian labels for boxed warnings. Among each group, the concordance between the two nations varied from 25% to 100%. The lowest concordance of 25% was observed on code B drug labels, and 100% concordance was observed on code J, M, R and S drug labels.

The PBW is more on Canadian labels (47%) than on USA labels (37%), which was similar to the PSI results. The same correlation between the PBW and PSI was also found in the previous study, which utilised new molecular entities among different countries (Shimazawa and Ikeda, 2013a). They suggested that the PBW is similar to the PSI because of the nature of the boxed warnings that are indicative of critical safety issues on a label. In another study, researchers found that 39% of the top selling drugs in 2012 possessed boxed warnings (Cheng PharmD et al., 2014). They have concluded that the boxed warnings are common among the drug labels.

3.4. Qualitative comparison of the product label information

After the comparison of the information provided in contraindications sections, boxed/serious warnings and overdose sections of the randomly selected labels, it was found that there are indeed real differences that existed between the labels. The comparison in Table 6 presents the results (online only Tables S4–S6).

Among the contraindications examined from the three countries, we have found differences in the information provided in the majority of the drug labels. Contraindications were similar in 31 cases out of 100 between the USA, the UK and Canada. The contraindications listed hypersensitivity reactions on the majority of labels. Dabigatran etexilate contraindications from Canada specify that the drug is contraindicated in nursing women, and this information is missing in the UK contraindications. Similar differences, especially in pregnancy, existed between labels of different countries on drug labels such as acarbose, pioglitazone, spironolactone, lisinopril, irbesartan, valsartan, finasteride, docetaxel, sunitinib, degarelix, mycophenolate, celecoxib, denosumab, and fentanyl. For the drug nilotinib, the contraindications section provided more contraindications, including QTc prolongation, hypokalemia or hypomagnesemia, in Canada when compared to the UK.

In the USA, there is a capitalised and bolded heading with the type of warning followed by a few sentences that describe this issue most frequently. However, in Canada there are only sentences that describe the issue under the serious warnings and precautions section. The heading in the USA boxed warnings is comparable to the text in the Canadian labels. The rest of the additional information provided is different, and more information is provided in the Canadian labels' 'serious warnings and precautions' section than on the USA labels (online only Table S5).

We went on to study the section related to overdose in the USA, the UK and Canada. Most of the Canadian labels contained text that suggests contacting the poison control in case of over-

Table 6

Number of drug labels out of 100 selected labels with similar information in the USA, the UK and Canada.

ATC code	A (n = 7)	B (n = 4)	C (n = 7)	D (n = 7)	G (n = 5)	H (n = 4)	J (n = 12)	L (n = 21)	M (n = 4)	N (n = 16)	R (n = 3)	S (n = 8)	V (n = 2)	All (n = 100)
Contraindications	3	1	1	3	1	2	6	1	1	5	2	4	1	31
Boxed/serious warnings	1	0	4	0	0	0	1	2	0	0	0	0	0	8
Overdosage	0	0	0	1	0	0	0	0	0	0	0	0	0	1

Abbreviations: ATC, Anatomical Therapeutic Chemical; A, alimentary tract and metabolism; B, blood and blood-forming organs; C, cardiovascular system; D, dermatologicals; G, genitourinary system and sex hormones; H, systemic hormonal preparations, excluding sex hormones; J, general anti-infectives for systemic use; L, antineoplastic and immunomodulating agents; M, musculo-skeletal system; N, nervous system; R, respiratory system; S, sensory organs; and V, various.

Similarity and difference was assessed manually by comparing each label.

Boxed/serious warnings were compared between USA and Canada.

dose. There are discrepancies in listing antidotes among the countries in some cases. In the case of ophthalmic olopatadine, an overdose section is not present in the USA label; the UK label describes oral overdose, but the Canadian label suggests flushing with warm water. This section is different in all three countries for the studied 100 drugs except one (online only Table S6). One previous study conducted on the inclusion of pharmacogenomics information on drug labels had also found differences among the labels from the USA, the UK and Japan (Shimazawa and Ikeda, 2013b). Our study suggests that the safety information is different among the USA, the UK and Canada. All these differences in qualitative data and the differences in volume are indicative of the differences in the actual message conveyed; however, validated studies are needed to confirm this statement.

4. Conclusion

There were significant differences in the drug labels' safety information among the USA, the UK and Canada by the same manufacturer. These differences could pose a risk to patients. The volume of the information on the drug labels is different for different countries. A larger volume of information might have poor readability and can lead to adverse reactions from the drugs. The information provided was also found to be different among countries. In fact, we have observed vast differences in the information provided on the labels of the same drug in different countries. Regulatory authorities need to make sure that enough safety information is provided on the label for the same therapeutic indications for all countries in which a drug is distributed.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.jsps.2017.07.006>.

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