PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Quality of medicines in Canada: a retrospective review of risk communication documents (2005–2013)
AUTHORS	Almuzaini, Tariq; Sammons, Helen; Choonara, Imti

VERSION 1 - REVIEW

REVIEWER	Joel Lexchin York University Canada
REVIEW RETURNED	14-Jul-2014

GENERAL COMMENTS	This is an interesting study and as the authors note the first of its kind in Canada however, I am unclear of the exact rational for undertaking this study. According to the authors, having studied this problem in the UK, they wanted to look at another HIC. Why did they want to look at another HIC? What was the rational for choosing Canada over say Australia or New Zealand? Did the authors have any a priori hypotheses about how Canada would compare to the UK? Although it appears that the authors wanted to compare the situation in Canada with that in the UK very little of the Discussion is devoted to comparing the two countries. The authors should expand on the comparison they offer and also provide background information on the drug regulatory systems in the UK and Canada so that readers can interpret any differences in the way that the countries detect and deal with substandard medicines. The authors state that Health Canada only started posting information about drug recalls on its web site in 2005 but there is actually information about safety issues going back to 1997 – see http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/search-recherche/simple?s=&plain_text=&f_sc=40&f_mc=3&js_en=&page=5&per_page=2525. The authors should note that not all safety problems are of equal concern. In addition, I have more specific comments. Page 3, line 51: What do the authors mean by "right decision"? Page 4, line 25: The search was not for defective medicines, it was for warnings that Health Canada had issued about defective medicines. Page 4, line 27: The URL for the web site should be given.

	Page 4, line 42: Define what "medicines recalled for regulatory reasons" means? Page 5, line 41: What do the authors mean by "significant problem"? Page 5, line 51: What is an "urgent recall"? Page 6, lines 35-54: While the information in this paragraph is interesting it would be even more interesting to know what percent of the all the products made by Apotex had stability issues, what percent of all products made by Baxter were contaminated, etc. Page 9, lines 43-45: What is the basis for this statement by the RCMP? Without knowing what type of data the RCMP is using for its statement it is not possible to know how accurate the statement is. Page 9, line 58: Define what a type 1, 2 and 3 notice is. Page 10, line 37: What do the authors mean by "pharmacovigilance data"? Page 10, line 50: Why do the authors say that this is a "significant problem"? What does “significant” mean? Finally, there are a number of places where there are minor grammatical errors that need to be corrected.

REVIEWER	Tim K. Mackey UC San Diego - School of Medicine California, USA The Partnership for Safe Medicines (PSM) is a nonprofit membership, dues driven organization of nonprofit public, private, academic, and patient entities supporting drug supply safety. TM is reimbursed for travel to one PSM annual conference each year. TM is independent of this source of funding. TM reports no other support from any organizations and no other financial relationships with any organizations that might have an interest in the submitted work.
REVIEW RETURNED	28-Jul-2014

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript that attempts to review drug recall and risk-communication documents from Health Canada to inform issues related to substandard and falsified medicines. ABSTRACT:

	-Objective: The objective is much too broad, this is a study looking at drug recall and risk communication documents from a national regulatory agency with the hopes of informing surveillance and reporting of substandard and falsified medicines though the results clearly indicate that falsified medicines were only a small proportion of the sample. This is really more a study about the current state of drug quality and safety in Canada than falsified medicines. Substandard medicines are the majority of the findings but should not be conflated with the issue of counterfeit/unapproved/falsified/fraudulent medicines. INTRODUCTION -pg. 3, para 1: There are not good studies determining the overall prevalence of falsified medicines in HIC, but there are plenty of case studies such as counterfeit Avastin in the USA etc. Also, again, there is a whole body of drug safety literature and recall/withdrawal literature on the topic of substandard medicines for HICs. Authors need to provide better context here for HICs. METHODS -p4, para 1: I wouldn't conflate "falsified" and call it "traditionally known as counterfeit". Instead, the piece should provide definitions of the terms up front and in a clear manner. If you are going to use "falsified" use the definitions that are now accepted in the literature. If you are going to use the term "counterfeit" use it throughout the manuscript but use the 1992 WHO definition. Use Attaran BMJ 2012 as this is a good resource. Also needs to be clarified that substandard is generally accepted as an "unintentional act" or error. Also, a more detailed description of the type of document Health Canada issues and how information was coded is necessary. -p4, para 2: Need to explain exclusion "medicines recalled for regulatory reasons" as this is pretty ambiguous as it stands -p5, para 2: Explain in more detail why ATC was used and how, I am unclear on the use of this secondary data source to classify defective medicines RESULTS -p5, para 3: Now you are using the term "defective medicines" again definitions really need to be consistently used even if describing a large category. Suggest you define defective medicines at first usage and also describe this as a broad category in your introduction then specify that you are examining sub-classes of substandard and falsified (which from your results looks like it comprises of the total of substandard + falsified). This is unclear now. -p5-6, para 5: Authors should insert "N" when reporting results. Authors collected recall class, so why not use it in the results section along with discussion about "urgently recalled" (which is itself not defined)? -p.6, para 3: Authors should give top line data here. What % (n=?) of all defective and substandard incidents were attributable to a licensed manufacturer? It looks like 399 based on your supplementary data, which would put it at over half the sample. What are the other half of the incidents, am I missing something? This is extremely important as it characterizes substandards in Canada. Are any other entities involved (e.g. distributors who do not package/store correctly leading to substandard quality?) -p.7, para 1: Not much in this falsified medicines section, only one therapeutic class and 2 proprietary products. I think this is why the main point of this manuscript should be an assessment of substandard medicines as this is the majority of the results. Authors also mention that they reviewed actions taken, in the context of falsified medicines, this information should be presented, and in my

	view also should be presented for substandards. DISCUSSION -p8, para 1: Wondering why HC is not reporting adverse events associated with these detections. Can authors provide more information? -p9, para 1-2: To include the discussion of falsified medicines prominently in this paper, authors need to further discuss the disconnect between case studies, news reports, etc. and very few falsified medicines detections by HC. Why are patient deaths not being reported in the adverse event reporting system, and though counterfeit medicines might be seized or detected, they may not be specifically intended for the domestic Canadian market, in this sense, it is unclear if they would be detected. Also, detection may occur outside of the more robust GMP inspections (e.g. detected among wholesale distributors) that may explain why falsified detections are so low. More discussion on this is necessary. -p9, para 3: Need to explain product notice 1-3. Additionally, authors have not included some key references on the subject that I provide below and should be incorporated: Ninan B, Wertheimer AI (2012) Withdrawing Drugs in the US Versus Other Countries. INNOVATIONS in pharmacy 3. Lexchin J (2012) New Drugs and Safety: What Happened to New Active Substances Approved in Canada Between 1995 and 2010? Arch Intern Med: 1–2. doi:10.1001/archinternmed.2012.4444 Mackey TK, Liang BA (2011) The global counterfeit drug trade: patient safety and public health risks. J Pharm Sci 100: 4571–4579. doi:10.1002/jps.22679. Overall, this is an interesting study, but needs a significant revision to reframe the piece for what it actually examined, substandard medicines primarily. Falsified medicines are such a small part of the sample though are an important part of the discussion. Authors should reframe on the topic of drug safety and recalls/withdraws in Canada, and then bring in discussion about falsified medicines as an additional data point. Also, the piece needs some copyediting for grammar and spelling in order to ensure readability.

VERSION 1 – AUTHOR RESPONSE

Reviewer's comment #1: This is an interesting study and as the authors note the first of its kind in Canada however, I am unclear of the exact rational for undertaking this study. According to the authors, having studied this problem in the UK, they wanted to look at another HIC. Why did they want to look at another HIC? What was the rational for choosing Canada over say Australia or New Zealand? Did the authors have any a priori hypotheses about how Canada would compare to the UK? Although it appears that the authors wanted to compare the situation in Canada with that in the UK very little of the Discussion is devoted to comparing the two countries. The authors should expand on the comparison they offer and also provide background information on the drug regulatory systems in the UK and Canada so that readers can interpret any differences in the way that the countries detect and deal with substandard medicines.

Authors' response: Thank you very much for your time in going over the manuscript and your valuable comments. The main purpose of this paper is to explore the problem in Canada as the problem has not been previously studied in this setting (please see the last sentence in the introduction, page 3). Our preliminary search revealed that Health Canada and the UK keep a comprehensive list of previous drug recalls and safety warnings concerning drug quality, compared with other HIC such as Australia and New Zealand. Therefore, their databases are more reliable.
Please see these links:

Australia:
http://www.tga.gov.au/safety/recalls-all-date.htm#.U-9qscVdWQA (the majority are natural health products and medical devices)
New Zealand:
http://www.medsafe.govt.nz/hot/RecallActionNoticesNew/RecallsActions.asp

As you suggested, relevant regulations concerning risk-communication documents and recalls have been incorporated. We have expanded our discussion to cover this point and compared the findings in both countries (please see the last paragraph on page 11 and the first two paragraphs on page 12).

Reviewer's comment #2: The authors state that Health Canada only started posting information about drug recalls on its web site in 2005 but there is actually information about safety issues going back to 1997 – see http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/search-recherche/simple?s=&plain_text=&f_sc=40&f_mc=3&js_en=&page=5&per_page=2525.

Authors' response: Before 2005, there were only two types of risk communication documents (public advisory and Dear Healthcare Professional letters) available on Health Canada's website. Health Product Recalls are the main tool that Health Canada uses to convey quality issues relating to medicines. Health Canada started posting these recalls in 2005, so we decided to start at 2005. Please see:
http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/search-recherche/simple?s=&plain_text=&f_sc=40&f_mc=3&js_en=&page=5&per_page=2350
We realise that this was not clearly explained in the previous version and it has now been added (please see the highlighted text in the third paragraph on page 5).

Reviewer's comment #3: The authors should note that not all safety problems are of equal concern.

Authors' response: We have clarified this now. Please see the definitions given for different risk communication documents on pages 4 and 5.

Reviewer's comment #4: Page 3, line 51: What do the authors mean by "right decision"?

Authors' response: We have amended the text for clarification. Please see the last sentence of the first paragraph, page 4.

Reviewer's comment #5: Page 4, line 25: The search was not for defective medicines, it was for warnings that Health Canada had issued about defective medicines.

Authors' response: We have edited the language to reflect your suggestion. Please see the first sentence in the third paragraph, page 5.

Reviewer's comment #6: Page 4, line 27: The URL for the web site should be given.

Authors' response: We have now added the link. Please see the highlighted text in the third paragraph, page 5.

Reviewer's comment #7: Page 4, line 42: Define what "medicines recalled for regulatory reasons" means?

Authors' response: We have edited the text for clarification. It now reads: "…..and other natural heath product recalled for regulatory reason (i.e., those do not have a valid marketing authorisation)".

Reviewer's comment #8: Page 5, line 41: What do the authors mean by "significant problem"?

Authors' response: We understand that significance has many different meanings including statistical significance. We therefore have changed the sentence to show that substandard medicines with stability issues were by far the largest group of substandard medicines seen. Please see the revised text in the second paragraph on page 7 and also see Table 1.

Reviewer's comment #9: Page 5, line 51: What is an "urgent recall"?

Authors' response: We have now defined the meaning of urgent communications and the relevant risk-communication documents used with it. Please see the highlighted text on pages 4 and 5.

Reviewer's comment #10: Page 6, lines 35-54: While the information in this paragraph is interesting it would be even more interesting to know what percent of the all the products made by Apotex had stability issues, what percent of all products made by Baxter were contaminated, etc.

Authors' response: We agree with the reviewer that it would be interesting to know the percent of each type of quality defect of the products made by each manufacturer. In order to do this, we need to work out the total number of units of every batch with stability issues recalled by Apotex, and the total number of units produced by Apotex in the study period (9 years). Unfortunately, this information was not provided by the manufacturers. However, we have tried to link the number of recalls to the size of the business of the relevant manufacturers in Canada by providing the total number of medicines marketed by each manufacturer (supplementary table 4).

Reviewer's comment #11: Page 9, lines 43-45: What is the basis for this statement by the RCMP? Without knowing what type of data the RCMP is using for its statement it is not possible to know how accurate the statement is.

Authors' response: We have reworded the whole section on falsified medicines and amended the language to reflect the above suggestion. The RCMP statement is now excluded; please see the discussion on falsified medicines, page 11.

Reviewer's comment #12: Page 9, line 58: Define what a type 1, 2 and 3 notice is.

Authors' response: We have defined these types in our revised manuscript. Please see the method section, first paragraph on page 5.

Reviewer's comment #13: Page 10, line 37: What do the authors mean by "pharmacovigilance data"?

Authors' response: We have amended the text to clarify the meaning; please see the limitation section on page 12.

Reviewer's comment #14: Page 10, line 50: Why do the authors say that this is a "significant problem"? What does "significant" mean?

Authors' response: We have changed this point to clarify that it is an increasing problem. Please look at the conclusion on page 12 and also Figure 2, which shows that the problem of substandard medicines is increasing in magnitude every year.

Reviewer's comment #15: Finally, there are a number of places where there are minor grammatical errors that need to be corrected.

Authors' response: Thank you very much; we have reviewed the paper and corrected the grammar where appropriate.

Reviewer: Tim K. Mackey, MAS, PhD(c)
Institution and Country UC San Diego - School of Medicine
California, USA

Reviewer's comment #1: ABSTRACT: (i) The objective is much too broad, this is a study looking at drug recall and risk communication documents from a national regulatory agency with the hopes of informing surveillance and reporting of substandard and falsified medicines though the results clearly indicate that falsified medicines were only a small proportion of the sample. This is really more a study about the current state of drug quality and safety in Canada than falsified medicines. (ii) Substandard medicines are the majority of the findings but should not be conflated with the issue of counterfeit/unapproved/falsified/fraudulent medicines.

Authors' response: Thank you very much for your constructive and helpful comments. (i) We have edited the study title and the objective both in the abstract and in the introduction to reflect the above suggestion. Please see the abstract, page 2, and the last paragraph in the introduction, page 4.
(ii) Although falsified medicines are part of our results, we agree with the reviewer that it is just small proportion of our findings and should not be conflated with substandard medicines. Therefore, we discussed both problems separately in the results and discussion sections. Moreover, we have significantly shortened the discussion allocated for falsified medicines in both the results and in the discussion.

Reviewer's comment #2: INTRODUCTION -pg. 3, para 1: There are not good studies determining the overall prevalence of falsified medicines in HIC, but there are plenty of case studies such as counterfeit Avastin in the USA etc. Also, again, there is a whole body of drug safety literature and recall/withdrawal literature on the topic of substandard medicines for HICs. Authors need to provide better context here for HICs.

Authors' response: We have edited this paragraph in accordance with your suggestions. Please see the last paragraph on page 3.

Reviewer's comment #3: METHODS -p4, para 1: (i) I wouldn't conflate "falsified" and call it "traditionally known as counterfeit". Instead, the piece should provide definitions of the terms up front and in a clear manner. If you are going to use "falsified" use the definitions that are now accepted in the literature. If you are going to use the term "counterfeit" use it throughout the manuscript but use the 1992 WHO definition. Use Attaran BMJ 2012 as this is a good resource. Also needs to be clarified that substandard is generally accepted as an "unintentional act" or error. (i) Also, a more detailed description of the type of document Health Canada issues and how information was coded is necessary.

Authors' response: (i) As you suggested, we have provided the definition of both substandard and falsified medicines and used the suggested reference (reference 8); please see the second paragraph of the introduction on page 3.
(ii) We have now described the documents that Health Canada uses for issues relating to drug quality. Please see the methods section pages 4 and 5.

Reviewer's comment #4: p4, para 2: Need to explain exclusion "medicines recalled for regulatory reasons" as this is pretty ambiguous as it stands.

Authors' response: We have clarified this in the revised version of the paper. It now reads: "……and other natural heath product recalled for regulatory reason (i.e., those do not have a valid marketing authorisation)".

Reviewer's comment #5: -p5, para 2: Explain in more detail why ATC was used and how, I am unclear on the use of this secondary data source to classify defective medicines

Authors' response: We wanted to inform the reader about different therapeutic classes of medicines affected by these recalls. It is difficult to present all 649 substandard medicines, so we used the ATC classification system. This system is controlled by the World Health Organization and categorises medicines according the organ or system in which these drugs act as well as according to their therapeutic classes. We thank the reviewer for pointing out this as we realised that it was not clearly mentioned in the previous version. It is now clarified; please see the third paragraph on pages 6.

Reviewer's comment #6: RESULTS- p5, para 3: Now you are using the term "defective medicines" again definitions really need to be consistently used even if describing a large category. Suggest you define defective medicines at first usage and also describe this as a broad category in your introduction then specify that you are examining sub-classes of substandard and falsified (which from your results looks like it comprises of the total of substandard + falsified). This is unclear now.

Authors' response: As you suggested, we have defined defective medicines in the introduction as a broad category that comprises both substandard and falsified medicines. Please see the second paragraph of the introduction on page 3.

Reviewer's comment #7:p5-6, para 5: (i) Authors should insert "N" when reporting results. (i) Authors collected recall class, so why not use it in the results section along with discussion about "urgently recalled" (which is Itself not defined)?

Authors' response: (i) We have now inserted "n" to indicate results.
(ii) We have now defined different risk communication documents. We have defined what Health Canada considers to be urgent communication, which requires urgent recall, and what Health Canada considers to be semi-urgent communication (please see the methods section on pages 4 and 5). Recall classes are part of the risk communication documents, which are called Health Product Recall types I, II and III. Type I, along with Public Warning document, are considered to be urgent communications. These are discussed separately in the third paragraph on page 7 and presented in tables 2 and 3. Health Product Recall types II and III, together with Public Advisory and Dear Healthcare Professional letters, are considered to be semi-urgent communications. We have now added a paragraph discussing semi-urgent communications on page 8 (paragraph 1) and a supplementary table (Table 2).

Reviewer's comment #8: -p.6, para 3: Authors should give top line data here. What % (n=?) of all defective and substandard incidents were attributable to a licensed manufacturer? It looks like 399 based on your supplementary data, which would put it at over half the sample. What are the other half of the incidents, am I missing something? This is extremely important as it characterizes substandards in Canada. Are any other entities involved (e.g. distributors who do not package/store correctly leading to substandard quality?)

Authors' response: All substandard medicines (n=649) were attributable to a licensed manufacturer or distributor. All together, this constitutes 122 manufacturers and 26 distributors. It was difficult to present all of them in our paper, thus we have now listed the top 20 manufacturers (supplementary table 4) responsible for 418 (64%) substandard medicines. We have now clarified this in the text

(please see the third and fourth paragraphs on page 8). We have also conducted a comparison between manufacturers and distributors in the number of substandard medicines reported under each type of quality defect. Please see the third paragraph on page 8, and Table 4.

Reviewer's comment #9: -p.7, para 1: Not much in this falsified medicines section, only one therapeutic class and 2 proprietary products. I think this is why the main point of this manuscript should be an assessment of substandard medicines as this is the majority of the results.

Authors' response: Please see our response to comment 1. As you suggested, we have now shortened the discussion on falsified medicines in this section.

Reviewer's comment #10: Authors also mention that they reviewed actions taken, in the context of falsified medicines, this information should be presented, and in my view also should be presented for substandards.

Authors' response: These documents are issued to communicate the message to the healthcare professionals and the public on the proper action that they can take. These documents don't convey the action that the Health Canada has undergone or subsequent investigations and arrests, especially with falsified medicines. We realised that we have not made this clear in the previous version and it now has been clarified. Please see the revised text in the first paragraph on page 6 and the second paragraph on page 9.

Reviewer's comment #11: DISCUSSION -p8, para 1: Wondering why HC is not reporting adverse events associated with these detections. Can authors provide more information?

Authors' response: This is an important question. Unfortunately, we were unable to find information regarding why Health Canada didn't report these adverse events.

Reviewer's comment #12: -p9, para 1-2: (i) To include the discussion of falsified medicines prominently in this paper, authors need to further discuss the disconnect between case studies, news reports, etc. and very few falsified medicines detections by HC. (ii) Why are patient deaths not being reported in the adverse event reporting system, and though counterfeit medicines might be seized or detected, they may not be specifically intended for the domestic Canadian market, in this sense, it is unclear if they would be detected. Also, detection may occur outside of the more robust GMP inspections (e.g. detected among wholesale distributors) that may explain why falsified detections are so low. More discussion on this is necessary.

Authors' response: (ii) As we found only a few falsified medicine detections by Health Canada, we wanted to see if there are any incidents of falsified medicines and case studies reported by other organisations in Canada that Health Canada missed reporting. However, on further consideration, we believe that this may create confusion and we have thus shortened the discussion in this section and focused on the main findings, substandard medicines. Case studies and news reports are now excluded. Please see the third paragraph on page 11.
(ii) We have now incorporated your suggestions in the discussion of this section. Please see the fourth paragraph on page 11.

Reviewer's comment #13: -p9, para 3: Need to explain product notice 1-3.

Authors' response: We have now defined Health Product recall types I, II and III in the methods section, first paragraph on page 5.

Reviewer's comment #14: Additionally, authors have not included some key references on the subject

that I provide below and should be incorporated:
Ninan B, Wertheimer AI (2012) Withdrawing Drugs in the US Versus Other Countries. INNOVATIONS in pharmacy 3.
Lexchin J (2012) New Drugs and Safety: What Happened to New Active Substances Approved in Canada Between 1995 and 2010? Arch Intern Med: 1–2. doi:10.1001/archinternmed.2012.4444
Mackey TK, Liang BA (2011) The global counterfeit drug trade: patient safety and public health risks. J Pharm Sci 100: 4571–4579. doi:10.1002/jps.22679.

Authors' response: The references above are now incorporated in the revised version of the manuscript (reference 4, 9 and 10).

Reviewer's comment #15: Overall, this is an interesting study, but needs a significant revision to reframe the piece for what it actually examined, substandard medicines primarily. Falsified medicines are such a small part of the sample though are an important part of the discussion. Authors should reframe on the topic of drug safety and recalls/withdraws in Canada, and then bring in discussion about falsified medicines as an additional data point.

Authors' response: We have tried to achieve this with our revised manuscript. Thank you for your suggestions for accomplishing this.

Reviewer's comment #16: Also, the piece needs some copyediting for grammar and spelling in order to ensure readability

Authors' response: Thank you; we have corrected the grammar where appropriate.

VERSION 2 – REVIEW

REVIEWER	Joel Lexchin York University, Canada
REVIEW RETURNED	27-Aug-2014

GENERAL COMMENTS	The authors have corrected some of the problems with the initial manuscript but there are still areas that require further work. Abstract, line 45: "Large" is a relative term – how are the authors using this term? Page 3, line 53: How are the authors using the term "significant"? Page 3, lines 55-57: In their reply to the reviewers the authors explained that they chose to look at Canada because of the level of publicly available data. This information should be incorporated into the text of the article. Page 5, lines 46-48: The authors need to be more specific about the dates, e.g., from January 1, 2005 to December 31, 2013. Page 5, lines 54-57:

	Did the authors exclude documents about products that had general safety issues (e.g., a new side effect was identified) as opposed to just a particular batch being falsified or substandard? Page 8, lines 38-39: The use of the term "no significant differences" implies that there was formal statistical testing. If so then the p value should be given. If there was no formal statistical testing then the wording should be changed. The authors need to provide some kind of explanation as to why they felt that manufacturers should be compared to distributors. Page 8, line 51: This should read that the concentration was either too high or too low. Page 10, line 5: Instead of "having" it should be "taking". Page 10, lines 6-11: Do the authors mean that the overdoses were due to the medication containing more active ingredient than was stated on the bottle? Page 10, line 29: The significance of the 1996 date needs to be explained. Was this the last time that Health Canada updated its GMP standards? Page 10, lines 32-36: This sentence is poorly worded. As it reads what is says is that the policy illustrates that the Good Manufacturing Policy is being complied with. More importantly, the increase in the number of incidents doesn't necessarily mean that Health Canada is doing a good job of enforcing its policies. It could also be that manufacturing practices are getting worse. Finally, the authors must make reference to the section of the 2011 Auditor General's report (Chapter 4) that discusses Health Canada's inspection program. Page 11, lines 19-21: Who would undertake these root cause investigations? Page 11, lines 42-46: Sales in Canada and the UK may be large in absolute dollars but each country represents only about 2% of the global market. Page 12, lines 10-16: The Canadian study was done over a 9 year period whereas the UK one was done over an 11 year period and therefore the difference is even larger than it appears. The authors also need to state the years of the UK review. Page 12, line 46:

	Once again the authors need to explain how they are using the term “large”. Figure 3: In addition to giving the absolute numbers the authors should also give the percentages to make it easier to compare the situation in Canada and the UK. Supplementary table 4: In the last two columns in addition to the absolute values being given the authors should also include percentages, e.g., then readers could see that Apotex has X% of all substandard medicines and makes Y% of all marketed medicines.

REVIEWER	Tim K Mackey UC San Diego, USA
REVIEW RETURNED	18-Sep-2014

GENERAL COMMENTS	The manuscript is much improved and authors have given a thorough and carefully constructed response. I have some minor suggestions for authors to consider but otherwise deem the manuscript acceptable for publication: p.3, s2: I would delete “enjoy robust” as arguably HICs lack sufficient post-market surveillance. p.8, first para: lowercase for “Majority” p.10, second para: is “correlated” the correct term here or “associated”?

VERSION 2 – AUTHOR RESPONSE

Reviewer: Joel Lexchin
Institution and Country: York University, Canada

Reviewer’s comment #1: Abstract, line 45: "Large" is a relative term – how are the authors using this term?

Authors’ response: We thank the reviewer for his valuable comments. The first sentence of the conclusion is now reworded excluding the word “large”.
It now reads: “Substandard medicines are a problem in Canada and have resulted in an increasing number of recalled medicines” (Page 2, lines 44-45)

Reviewer’s comment #2: Page 3, line 53: How are the authors using the term "significant"?

Authors’ response: We have amended the text to clarify the meaning. It now reads: “The study showed that substandard medicines are a problem that appears to be increasing” (Page 3, lines 54-55)

Reviewer’s comment #3: Page 3, lines 55-57: In their reply to the reviewers the authors explained that they chose to look at Canada because of the level of publicly available data. This information should

be incorporated into the text of the article.

Authors' response: As suggested, we have added this to the introduction.
It now reads: "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." (Page 4, lines 3-4)

Reviewer's comment #4: Page 5, lines 46-48: The authors need to be more specific about the dates, e.g., from January 1, 2005 to December 31, 2013.

Authors' response: We have now specified the dates. It now reads: "Therefore, the search was started from 2005, and all risk communication documents issued between 1 January 2005 and 31 December 2013 were included." (Page 5, lines 52-53)

Reviewer's comment #5: Page 5, lines 54-57: Did the authors exclude documents about products that had general safety issues (e.g., a new side effect was identified) as opposed to just a particular batch being falsified or substandard?

Authors' response: All risk-communication documents concerning medicines that acquired safety issues were excluded. Only those that conveyed quality issues were included. We thank the reviewer for pointing out this, as we realised that it was not clarified enough in the previous version. It now has been clarified. It now reads: "…and exclusion criteria were as follows: veterinary medicines; medicines lacking efficacy or acquiring general safety issues; herbal and probiotic products;… " (Page 6, lines 5-6)

Reviewer's comment #6: Page 8, lines 38-39: (i) The use of the term "no significant differences" implies that there was formal statistical testing. If so then the p value should be given. If there was no formal statistical testing then the wording should be changed. (ii)The authors need to provide some kind of explanation as to why they felt that manufacturers should be compared to distributors.

Authors' response:
(i) We compared the manufacturers to the distributors in regard to the number of substandard medicines reported under seven different types of quality defects. Therefore, the seven p values are presented in Table 4; all are insignificant. We believe that presenting these p values in the text will not help the article in terms of readability, as all of these p values have already been presented in Table 4. However, we would certainly be willing to add this information if it is still considered important. We have now amended the text to refer to these p values in the table.
It now reads: "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." (Page 8, lines 45-50)
(ii) We have explained this now.
It reads: "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." (Page 7, lines 5-10)

Reviewer's comment #7: Page 8, line 51: This should read that the concentration was either too high or too low.

Authors' response: We have amended the text according to your suggestion. It now reads: "Products of Sandoz Canada Inc. had a problem with the active ingredient; the concentration was either too high or too low" (Page 9, lines 3-4)

Reviewer's comment #8: Page 10, line 5: Instead of "having" it should be "taking".

Authors' response: We have used the suggested word "taking". (Page 10, line 19)

Reviewer's comment #9: Page 10, lines 6-11: Do the authors mean that the overdoses were due to the medication containing more active ingredient than was stated on the bottle?

Authors' response: We have now clarified our meaning in the text. It now reads: "However, owing to the lack of sufficient details, it was impossible to link the overdose events specifically to the substandard tablets." (Page 10, lines 26-29)

Reviewer's comment #10: Page 10, line 29: The significance of the 1996 date needs to be explained. Was this the last time that Health Canada updated its GMP standards?

Authors' response: Subsequent regulation and agreements took place since 1996 and led Health Canada to update its policy on GMP inspection (GMP Inspection Policy for Canadian Drug Establishments (POL-0011)). These include the introduction of Division 1A pertaining to drug establishment licensing; the recognition of Canada as a partner of the pharmaceutical inspection co-operation scheme in 1999; and the signing of Mutual Recognition Agreements by Canada with the European Union, Switzerland, Australia, New Zealand, the United States and Japan. We do not think a full description of these helps the article in its discussion length, but would be willing to add if this was still felt important.
We have also edited the language to clarify that the update was for the GMP inspection program but not for GMP guidelines, as the latter is constantly updated. It now reads: "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." (Page 10, lines 43-48)

Reviewer's comment #11: Page 10, lines 32-36: (i) This sentence is poorly worded. As it reads what is says is that the policy illustrates that the Good Manufacturing Policy is being complied with. (ii) More importantly, the increase in the number of incidents doesn't necessarily mean that Health Canada is doing a good job of enforcing its policies. It could also be that manufacturing practices are getting worse. (iii)Finally, the authors must make reference to the section of the 2011 Auditor General's report (Chapter 4) that discusses Health Canada's inspection program.

Authors' response: (i) We have now edited the language to reflect the intended meaning. It now reads: "The GMP policy illustrates the procedures Health Canada follows to ensure that all drug establishments comply with GMP guidelines." (Page 10, lines 55-57)
(i) We agree with the reviewer that the increase in the number of incidents may also be due to substandard manufacturing practices, and we have therefore incorporated this suggestion. Please see the last sentence of the first paragraph on page 11.
(iii) This reference has been added, reference no. 20.

Reviewer's comment #12: Page 11, lines 19-21: Who would undertake these root cause investigations?

Authors' response: When a company voluntarily decides, or is asked by Health Canada, to recall its defective medicine, the company must notify and collect information for Health Canada about the recalled medicine, including the root cause for the defect. It is the responsibility of Health Canada represented by its inspectorate to investigate and verify the root cause of the defect as well as to ensure that the company has taken corrective action to prevent similar episodes in the future. We

have now incorporated this information in the text.
It reads: “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” (Page 11, lines 49-57)

Reviewer’s comment #13: Page 11, lines 42-46: Sales in Canada and the UK may be large in absolute dollars but each country represents only about 2% of the global market.

Authors’ response: We agree. This has been incorporated to the discussion. It now reads: “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.” (Page 12, lines 31-34)

Reviewer’s comment #14: Page 12, lines 10-16: The Canadian study was done over a 9 year period whereas the UK one was done over an 11 year period and therefore the difference is even larger than it appears. The authors also need to state the years of the UK review.

Authors’ response: We agree with the reviewer. We have now stated the study period of the UK review and stated that the difference in the number of substandard medicines may be larger than it appears. It now reads: “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.” (Page 13, lines 8-13)

Reviewer’s comment #15: Page 12, line 46: Once again the authors need to explain how they are using the term “large”.

Authors’ response: We have edited the language to reflect that substandard medicines are an increasing problem. The term “large” is now excluded. It reads: “Substandard medicines are a problem in Canada and have resulted in an increasing number of recalled medicines.” (Page 13, lines 42-43)

Reviewer’s comment #16: Figure 3: In addition to giving the absolute numbers the authors should also give the percentages to make it easier to compare the situation in Canada and the UK.

Authors’ response: The percentages have been now given. Please look at Figure 3.

Reviewer’s comment #17: Supplementary table 4: In the last two columns in addition to the absolute values being given the authors should also include percentages, e.g., then readers could see that Apotex has X% of all substandard medicines and makes Y% of all marketed medicines.

Authors’ response: Thanks for pointing this out. We have given the percentages of the substandard medicines produced by each manufacturer, as we know the total number of substandard medicines reported by Health Canada (i.e., 649). Please see Supplementary table 4.
Unfortunately, some manufacturers do not provide their catalogues of marketed medicines in Canada. As a result, we could not determine the total number of marketed medicines in Canada and, consequently, are unable to calculate the parentage of marketed medicines by each manufacturer.

Reviewer: Tim K. Mackey, MAS, PhD(c) Institution and Country UC San Diego - School of Medicine California, USA

Reviewer's comment #1: p.3, s2: I would delete "enjoy robust" as arguably HICs lack sufficient post-market surveillance.

Authors' response: Thanks for the comments. We have edited this sentence according to your suggestion. It now reads as follows: "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." (Page 3, lines 38-43)

Reviewer's comment #2: p.8, first para: lowercase for "Majority"

Authors' response: We have edited the word. (Page 8, line 20)

Reviewer's comment #3:p.10, second para: is "correlated" the correct term here or "associated"?

Authors' response: We have changed the term "correlated" to "associated", as we believe, on further consideration, this is the best term fits within the context. (Page 10, line 38)