## PEER REVIEW HISTORY



## ARTICLE DETAILS

| | |
|---|---|
| **TITLE (PROVISIONAL)** | Public health concerns for anti-obesity medicines imported for personal use through the Internet: a cross-sectional study |
| **AUTHORS** | Mohiuddin Hussain Khan, Tsuyoshi Tanimoto, Yoko Nakanishi, Naoko Yoshida, Hirohito Tsuboi and Kazuko Kimura |

## VERSION 1 - REVIEW

| | |
|---|---|
| **REVIEWER** | Shunsuke Ono<br>Associate Professor<br>University of Tokyo<br>Japan |
| **REVIEW RETURNED** | 30/01/2012 |

| | |
|---|---|
| **THE STUDY** | This is not a clinical research paper and I cannot evaluate from the perspectives above. I am afraid this manuscript is not within the scope and aim of the Journal. |
| **RESULTS & CONCLUSIONS** | This is not a clinical research paper. I am afraid this manuscript is not within the scope and aim of the Journal. |
| **REPORTING & ETHICS** | This is not a clinical research paper, and I cannot judge from the aspects above. |
| **GENERAL COMMENTS** | Overall:<br>I cannot tell if the issues provided in this manuscript are within the aim and scope of this journal. The journal's format of abstract is apparently for clinical studies, and the content of this paper does not fit well the abstract format.<br>Because the sampling of drugs was done fairly arbitrarily, not systematically, and response rates of manufacturers are low, it is difficult to call this research rigorous cross-sectional survey (although it is not a longitudinal study by definition).<br><br>P5, l64-72: The context of these statements is unclear. It is important to clarify what country(ies) and what kind of population these explanations are aimed at.<br><br>P6, l89-97: The authors have to explain why and in what sense this research adds to the findings in previous studies.<br><br>P7, l115: It is not clearly stated how the samples were collected. Is that done randomly, systematically to achieve some objective? or, just arbitrarily? Can the authors justify how they collected samples? Please explain.<br><br>P11, l184: Please explain why the authors concluded the Cialis, Levitra and Viagra explained here were counterfeit. There is no explanation how to tell them authentic from counterfeit for these drugs in the text. There is no definition of 'counterfeit' or 'fake', either. |

| | |
|---|---|
| | P17, l272: The authors have to explain how the advertisement from outside Japan via Internet is regulated or handled in the regulation. It should also be mentioned to what extent the Japanese government has jurisdiction over such cross-border advertisement and marketing. |

| | |
|---|---|
| **REVIEWER** | Budiono Santoso, MD, PhD<br>Team Leader, Essential Medicines & Health technologies,<br>World Health Organization |
| **REVIEW RETURNED** | 02/02/2012 |

| | |
|---|---|
| **GENERAL COMMENTS** | This is one of rare publication on the issue of medicines quality distributed through internet. The work provides a valuable information that counterfeit medicines also penetrates the distribution channel through internet |

| | |
|---|---|
| **REVIEWER** | Timothy Ken Mackey, MAS<br>Senior Research Associate<br>Institute of Health Law Studies |
| **REVIEW RETURNED** | 09/02/2012 |

| | |
|---|---|
| **THE STUDY** | Note: For those categories that are not applicable I have marked "yes"<br><br>Abstract: After reading the article I think the results really need to be better organized. I think what is important is out of the 82 samples how many were tested and how many did not receive a response from the manufacturer? (I am still not clear on this after multiple reads) Also, you may want to identify that counterfeits were represented as orlistat.<br><br>Methods:<br>Selection: I think there should be more information in the methods section including: (1) the Japanese characters (either kanji, katakana, hiragana, etc.) that were used in the search and not just the translated search words; (2) the methodology is largely unclear and unorganized, how many pages of search results were included? what was the specific inclusion/exclusion criteria for sites (were all sites that used a Japan or US address excluded as they were deemed safer?); (3) I am completely unclear on how sites were "prioritized", wouldn't it just be easier to list the frequency of anti-obesity drugs offered in total searches?; (4) would really like to know the n size on how many sites were assessed, excluded, and included. Please also explain what the ASCT is and why it is pertinent to this discussion. Perhaps you should also list all anti-obesity drugs identified as available for sale in a separate figure?<br>Observational Analysis: Confused on why "Japanese manual" is included in this section? Did products include a Japanese manual with packaging?<br>Preparation of the sample solutions: Would be helpful to list out the samples prepared in a separate table suggested above.<br>Authenticity Investigation: How do the catalogue and questionnaire differ from the information taken during the observational analysis? Did this information feed into what was provided to the manufacturers for authenticity check? |

| | |
|---|---|
| | Standard of English is acceptable, but there are minor typos and grammatical errors that should be proofread and corrected throughout.<br><br>Reference: There are many other references regarding the characteristics and makeup of internet sites that are not referenced and would lend to providing background to the piece: Orizio G, Rubinelli S, Schulz PJ, Domenighini S, Bressanelli M, Caimi L, Gelatti U. "Save 30% if you buy today". Online pharmacies and the enhancement of peripheral thinking in consumers. Pharmacoepidemiol Drug Saf. 2010 Sep;19(9):970-6. PMID: 20652863.; Orizio G, Merla A, Schulz PJ, Gelatti U. Quality of online pharmacies and websites selling prescription drugs: a systematic review. J Med Internet Res. 2011 Sep 30;13(3):e74. PMID: 21965220; Liang BA, Mackey T. Searching for safety: addressing search engine, website, and provider accountability for illicit online drug sales. Am J Law Med. 2009;35(1):125–184. PMID: 19534258; |
| **RESULTS & CONCLUSIONS** | Are they well presented?: I think there is no need to mention in the characteristics of the sites if they also advertised ED drugs. I think this distracts from the main research findings of the article, the prevalence of counterfeit anti-obesity drugs. Would be better to provide more detailed description on the varieties of anti-obesity products identified and other characteristics of online pharmacies identified (i.e. purported country of origin, advertising "no prescription" [is this 100%?], etc.) Again, more explanation of what type of credentialing ASCT offers would be helpful for readers. Is this specific to medical products sold online or to e-commerce sites in general?<br>Information provided with samples: Please report n numbers in these stats.<br>Shipment of the samples: I think the findings in this section are very important, in that they show sourcing is occurring in multiple countries and a great deal of misrepresentation regarding declaring packages is being made. It would be helpful to know how Japanese custom officials treat these declarations and how they are investigated.<br>Sample characteristics: Were these drugs also advertised by their brand names (i.e. meridia, alli, etc.?) Might also help to discuss that rimonabant was removed from the market. I am also unclear why lovastatin and rhubarb are discussed as they do not seem applicable to anti-obesity treatment (lovastatin is a statin for lowering of cholesterol, so I wouldn't classify it as an anti-obesity drug). Is this off-label use? I would make clearer the results of this section in a table.<br><br>Quality analysis: Sorry I am unclear, I thought that there were 43 samples of product with sibutramine hydrochloride not 21 and 15 orlistat samples not 13? Were only select samples examined?<br><br>Authenticity Investigation: I am unclear what is meant by "country of authorized marketer" do you mean the manufacturer of the product or the website marketer? Obviously it seem unlikely that Switzerland would be the source country for a counterfeit medicine but if this is the case, please clarify.<br><br>Conclusions: There should be more discussion of the results from the ED study in Japan supported by the MOH to fit a pattern. Also, there is abundant literature detailing the presence of adulterated and counterfeit products, especially for anti-malarials that the authors could discuss as previous evidence of worrying trends (as partially |

| | |
|---|---|
| | discussed in reference #37). I'd like more discussion about the policy implications of advertising drugs on the Internet that are unapproved and the legality of marketing these products online. Also what are the statutory penalties for violating these laws and are there any enforcement mechanisms/are they adequate? This would help in formulating potential solutions. |
| **GENERAL COMMENTS** | Thank you for the opportunity of reviewing this manuscript and I am personally excited to be part of open peer review. I think this piece provides extremely important data on the characteristics of online pharmacies selling counterfeit drugs. This includes information on website characteristics, shipping/customs information, packaging, and chemical assays of quality. The article contains important empirical evidence of counterfeit medicines in the drug supply chain and accessibility of high-income countries such as Japan that also enjoy national health systems and more universal access to clinical care. These are important findings that require public attention, patient education and further research.<br><br>That said, I fear the article suffers from disorganization and lack of clarity in the methodology, research results and very sparse discussion about the implications of these findings (as outlined in other comments). All these areas of the manuscript should and need to be improved in order to make this piece suitable for publication.<br><br>Other minor comments:<br><br>Abstract: I think it would be helpful to clarify that all medicines purchased required a prescription to dispense.<br><br>Introduction: I think the introduction should give a bit more focus on the burgeoning problem of online pharmacies in Japan specifically, including the cited study on ED drugs done by the MOH. This would provide better background into this problem in country. Perhaps also some discussion of why other anti-obesity medicines have not been approved in Japan. Is it their safety profile, risk v. benefit, cost effectiveness, etc? Also, in the second paragraph it is mentioned that "lifestyle medicines" are frequently targeted by counterfeiters, but I would argue that this is far too narrow in scope. In fact, all types of therapeutic classes of medicines are counterfeited from essential medicines to lifestyle drugs. I think this should be stated. Also, I'm not sure that given the severity of obesity and related conditions/co morbidities, that the authors should make any word connection with "lifestyle medicines" which usually fall under the connotation of drugs like ED drugs. Helpful reference includes: The global counterfeit drug trade: patient safety and public health risks. Mackey TK, Liang BA. J Pharm Sci. 2011 Nov;100(11):4571-9. doi: 10.1002/jps.22679. Epub 2011 Jun 22 and The global threat of counterfeit drugs: why industry and governments must communicate the dangers. Cockburn R, Newton PN, Agyarko EK, Akunyili D, White NJ. PLoS Med. 2005 Apr;2(4):e100. Epub 2005 Mar 14.<br><br>Some minor grammatical issues:<br>"Strength and Limitations" : "are a must" not "are must"; "Alli" is spelled wrong |

**VERSION 1 – AUTHOR RESPONSE**

Responses on Reviewers' Comments

Reviewer: Shunsuke Ono
Associate Professor
University of Tokyo
Japan

Overall:
I cannot tell if the issues provided in this manuscript are within the aim and scope of this journal. The journal's format of abstract is apparently for clinical studies, and the content of this paper does not fit well the abstract format.
Because the sampling of drugs was done fairly arbitrarily, not systematically, and response rates of manufacturers are low, it is difficult to call this research rigorous cross-sectional survey (although it is not a longitudinal study by definition).

Response: Thanks so much for reviewing of our manuscript and your valuable comments. In our opinion, according to aim and scopes of the BMJ Open, stated at http://bmjopen.bmj.com/site/about/resources/aimsandscope.xhtml, our manuscript might be considered for publication. In our opinion, the prescribed abstract format of the journal may prioritize clinical studies; however, we well adapted our abstract fitting into the format.

A multi-stage sampling scheme was followed in the sampling of our study, where selection of the Internet sites was done purposively and the sampling of medicines conducted according to certain sampling criteria. We edited methods section for better understanding at lines 123 – 150 and changed 'cross-sectional survey' into 'cross-sectional study' at line 2 in the title and at line 18 of the abstract.

P5, l64-72: The context of these statements is unclear. It is important to clarify what country(ies) and what kind of population these explanations are aimed at.
Response: The statements at lines 64-72 aimed at firstly providing evidences of using the Internet for health related issues among general adult population of developed countries like Japan and USA. We have edited texts at lines 64 – 71 and added references 3 and 4 at line 66 in the revised version of the manuscript for better clarification.

P6, l89-97: The authors have to explain why and in what sense this research adds to the findings in previous studies.
Response: So far, we did not find any reports on the quality of online anti-obesity medicines in Japan and on their circulation. We believe that this study may add these new information. We added texts at lines 104 - 110 accordingly.

P7, l115: It is not clearly stated how the samples were collected. Is that done randomly, systematically to achieve some objective? or, just arbitrarily? Can the authors justify how they collected samples? Please explain.
Response: As mentioned above, the samples were collected in a multistage sampling technique based on our previous research experiences on online medicines. The first stage of the sampling was done purposively for investigational purpose and the second stage was conducted according to some selection criteria. The sampling scheme may limit study findings to suspicious online pharmaceutical sites and we have admitted this fact in the discussion section at lines 391 – 393 as limitations. We edited texts at lines 123 – 150 to clarify sampling methods.

P11, l184: Please explain why the authors concluded the Cialis, Levitra and Viagra explained here were counterfeit. There is no explanation how to tell them authentic from counterfeit for these drugs in the text. There is no definition of 'counterfeit' or 'fake', either.

Response: Counterfeit Cialis and Levitra were identified and characterized by the Ministry of Health, Japan. However, we tried not to disclose these information from being published. Because of the worry that counterfeiters may also modify their strategies after reading these facts in details. We edited texts at lines 137 – 139 and added a reference (33) in this regard. The webpage contains photos and information on genuine and counterfeit products. Moreover, we mentioned definition of counterfeit medicines at lines 73 – 76 in the revised version of the manuscript.

P17, l272: The authors have to explain how the advertisement from outside Japan via Internet is regulated or handled in the regulation. It should also be mentioned to what extent the Japanese government has jurisdiction over such cross-border advertisement and marketing.
Response: We think it is still a challenge in many countries, not only in Japan, how illegal internet sites could be regulated from inside national boundaries. However, we believe that international collaborative approach may provide better control over the situation. We added new texts at lines 382 – 388 and at lines 404 – 409 in this regard.

Reviewer: Budiono Santoso, MD, PhD
Team Leader, Essential Medicines & Health technologies,
World Health Organization
Western Pacific Regional Office,
Manila, the Philippines.
This is one of rare publication on the issue of medicines quality distributed through internet. The work provides a valuable information that counterfeit medicines also penetrates the distribution channel through internet
Response: Thank you so much for the comments.

Reviewer: Timothy Ken Mackey, MAS
Senior Research Associate
Institute of Health Law Studies
San Diego, CA USA

Joint Doctoral Program in Global Health
University of California, San Diego - San Diego State University
San Diego, CA USA

Abstract: After reading the article I think the results really need to be better organized. I think what is important is out of the 82 samples how many were tested and how many did not receive a response from the manufacturer? (I am still not clear on this after multiple reads) Also, you may want to identify that counterfeits were represented as orlistat.
Response: We are grateful for your constructive comments. Texts at lines 29-33 in the abstract are edited according to the above suggestions. Additionally, we included the information in the result section at lines 288 – 290.

Methods:
Selection: I think there should be more information in the methods section including: (1) the Japanese characters (either kanji, katakana, hiragana, etc.) that were used in the search and not just the translated search words; (2) the methodology is largely unclear and unorganized, how many pages of search results were included? what was the specific inclusion/exclusion criteria for sites (were all sites that used a Japan or US address excluded as they were deemed safer?); (3) I am completely unclear

on how sites were "prioritized", wouldn't it just be easier to list the frequency of anti-obesity drugs offered in total searches?; (4) would really like to know the n size on how many sites were assessed, excluded, and included. Please also explain what the ASCT is and why it is pertinent to this discussion. Perhaps you should also list all anti-obesity drugs identified as available for sale in a separate figure?
Response: (1) We incorporated Japanese characters of keywords (at lines 123-149), (2) and edited methods section with more information. An approximate numbers of search results have been included. We excluded sites with physical address based on our experiences of our previous research findings that sites those conceal their physical address are more likely to offer counterfeits. (3) Actually, the available medicines displayed in the selected sites were numbered consecutively (1,2,3….). We edited the texts at lines 147 - 149 in this regard.
(4) In the first step, 15 sites were selected after checking first 500 search results. In the second step, six sites were selected for the sample purchase from first 100 search results. In the third step, two sites were selected out of 100 results. In the fourth step, samples purchased from nine sites and in the fifth step sample purchased from four sites out of 10. As mentioned, we edited methods section at lines 123 – 149 accordingly. An Explanation on ASCT has been provided at lines 156 – 161. We included a figure at line 219 on available items offered at the selected internet sites.

Observational Analysis: Confused on why "Japanese manual" is included in this section? Did products include a Japanese manual with packaging?
Response: Some of the products include information or notes in Japanese inside outer packaging. We edited the term as ‘Japanese information/notes’ at lines 167 and added package insert separately.

Preparation of the sample solutions: Would be helpful to list out the samples prepared in a separate table suggested above.
Response: Since, preparation methods of sample solution are almost similar, we only edited the texts in between lines 172 - 176 and 182 – 185. However, we included a list of all products that were sampled in table 1 at page 14, line 226.

Authenticity Investigation: How do the catalogue and questionnaire differ from the information taken during the observational analysis? Did this information feed into what was provided to the manufacturers for authenticity check?
Response: Yes. The catalogue is basically a database created on the basis of observation of all the samples. And the questionnaire is a generic set of questions prepared for manufacturers and medicine regulatory authorities. Information on a particular sample from the catalogue fed into the generic questionnaire to personalize the questionnaire to a specific manufacturer and for a particular sample before sending.

Standard of English is acceptable, but there are minor typos and grammatical errors that should be proofread and corrected throughout.

Reference: There are many other references regarding the characteristics and makeup of internet sites that are not referenced and would lend to providing background to the piece: Orizio G, Rubinelli S, Schulz PJ, Domenighini S, Bressanelli M, Caimi L, Gelatti U. "Save 30% if you buy today". Online pharmacies and the enhancement of peripheral thinking in consumers. Pharmacoepidemiol Drug Saf. 2010 Sep;19(9):970-6. PMID: 20652863.; Orizio G, Merla A, Schulz PJ, Gelatti U. Quality of online pharmacies and websites selling prescription drugs: a systematic review. J Med Internet Res. 2011 Sep 30;13(3):e74. PMID: 21965220; Liang BA, Mackey T. Searching for safety: addressing search engine, website, and provider accountability for illicit online drug sales. Am J Law Med. 2009;35(1):125–184. PMID: 19534258;
Response: Thank you so much for suggesting these references. We have edited texts throughout our

manuscript and added suggested references at lines 78 – 83, 345 and 388.

Are they well presented?: I think there is no need to mention in the characteristics of the sites if they also advertised ED drugs. I think this distracts from the main research findings of the article, the prevalence of counterfeit anti-obesity drugs. Would be better to provide more detailed description on the varieties of anti-obesity products identified and other characteristics of online pharmacies identified (i.e. purported country of origin, advertising "no prescription" [is this 100%?], etc.) Again, more explanation of what type of credentialing ASCT offers would be helpful for readers. Is this specific to medical products sold online or to e-commerce sites in general?
Response: We provided the suggested information in Table 1 at line 226 and more detailed information at lines 275 – 285. As mentioned above, we added explanation on ASCT in the methods section at lines 156 – 161.

Information provided with samples: Please report n numbers in these stats.
Response: As suggested, we revised texts at lines 243 – 248.

Shipment of the samples: I think the findings in this section are very important, in that they show sourcing is occurring in multiple countries and a great deal of misrepresentation regarding declaring packages is being made. It would be helpful to know how Japanese custom officials treat these declarations and how they are investigated.
Response: We agree with the comments that it would be really good to know practices of Japanese custom officials in such circumstances. However, this particular study was not designed comprehensively enough to evaluate these important areas, hence, further studies might be required. We added this limitation at line 393 in the discussion.

Sample characteristics: Were these drugs also advertised by their brand names (i.e. meridia, alli, etc.?) Might also help to discuss that rimonabant was removed from the market. I am also unclear why lovastatin and rhubarb are discussed as they do not seem applicable to anti-obesity treatment (lovastatin is a statin for lowering of cholesterol, so I wouldn't classify it as an anti-obesity drug). Is this off-label use? I would make clearer the results of this section in a table.
Response: Yes, these drugs were advertised by their brand names. We incorporated this information at line 269. We added new texts on withdrawal of rimonabant at lines 359 – 361 in the discussion section. We agree that lovastatin and rhubarb do not belong to anti-obesity medicines. As lovastatin and rhubarb were found under diet (ダイエット) search, we sampled these medicines. We indicated this clarification in Table 1 (**) of the revised version of the manuscript.

Quality analysis: Sorry I am unclear, I thought that there were 43 samples of product with sibutramine hydrochloride not 21 and 15 orlistat samples not 13? Were only select samples examined?
Response: We could not analyze 30 samples due to insufficient materials. We revised texts at lines 288 – 291 to make it clear.

Authenticity Investigation: I am unclear what is meant by "country of authorized marketer" do you mean the manufacturer of the product or the website marketer? Obviously it seem unlikely that Switzerland would be the source country for a counterfeit medicine but if this is the case, please clarify.
Response: We replaced words, ‘country of authorized marketer’ to ‘labeled country of marketing authorization holder’ in Table 2, at line 310 and we meant the manufacturer/marketer of the original products as found in the product labels. Because of the fact that from the labels of any counterfeit product, we could only know the origin of original similar products, and not the origin of counterfeit ones. So when, a product is identified as counterfeit, it might have originated in a country different from its labeled country.

Conclusions: There should be more discussion of the results from the ED study in Japan supported by the MOH to fit a pattern. Also, there is abundant literature detailing the presence of adulterated and counterfeit products, especially for anti-malarials that the authors could discuss as previous evidence of worrying trends (as partially discussed in reference #37). I'd like more discussion about the policy implications of advertising drugs on the Internet that are unapproved and the legality of marketing these products online. Also what are the statutory penalties for violating these laws and are there any enforcement mechanisms/are they adequate? This would help in formulating potential solutions.
Response: Actually, the reference of MOH on ED is a kind of warning based on two case investigations. We provided more information in this regard at lines 104 – 110. However, detailed characteristics of ED drugs were not discussed due to confidentiality and worries that counterfeiters may become aware and change their strategies. We briefly discussed penalties for violating laws in the discussion section at lines 382 – 388 and at lines 406 – 411 in the conclusion.

Thank you for the opportunity of reviewing this manuscript and I am personally excited to be part of open peer review. I think this piece provides extremely important data on the characteristics of online pharmacies selling counterfeit drugs. This includes information on website characteristics, shipping/customs information, packaging, and chemical assays of quality. The article contains important empirical evidence of counterfeit medicines in the drug supply chain and accessibility of high-income countries such as Japan that also enjoy national health systems and more universal access to clinical care. These are important findings that require public attention, patient education and further research.

That said, I fear the article suffers from disorganization and lack of clarity in the methodology, research results and very sparse discussion about the implications of these findings (as outlined in other comments). All these areas of the manuscript should and need to be improved in order to make this piece suitable for publication.

Response: Thanks so much for the appreciation. We tried our best to reorganize our manuscript and incorporate more information as suggested.

Other minor comments:

Abstract: I think it would be helpful to clarify that all medicines purchased required a prescription to dispense.
Response: Texts edited at lines 271 – 272 in this regard.

Introduction: I think the introduction should give a bit more focus on the burgeoning problem of online pharmacies in Japan specifically, including the cited study on ED drugs done by the MOH. This would provide better background into this problem in country. Perhaps also some discussion of why other anti-obesity medicines have not been approved in Japan. Is it their safety profile, risk v. benefit, cost effectiveness, etc? Also, in the second paragraph it is mentioned that "lifestyle medicines" are frequently targeted by counterfeiters, but I would argue that this is far too narrow in scope. In fact, all types of therapeutic classes of medicines are counterfeited from essential medicines to lifestyle drugs. I think this should be stated. Also, I'm not sure that given the severity of obesity and related conditions/co morbidities, that the authors should make any word connection with "lifestyle medicines" which usually fall under the connotation of drugs like ED drugs. Helpful reference includes: The global counterfeit drug trade: patient safety and public health risks. Mackey TK, Liang BA. J Pharm Sci. 2011 Nov;100(11):4571-9. doi: 10.1002/jps.22679. Epub 2011 Jun 22 and The global threat of counterfeit drugs: why industry and governments must communicate the dangers. Cockburn R, Newton PN, Agyarko EK, Akunyili D, White NJ. PLoS Med. 2005 Apr;2(4):e100. Epub 2005 Mar 14.
Response: Actually the report of MOH on ED drugs were based one two case investigations and only

provides information of the characteristics of counterfeits detected on the incidents. However, we edited texts at lines 104 – 110 and 137 – 139 to incorporate more information on ED studies in Japan. As suggested, we changed our previous texts into “since, all types of therapeutic classes of medicines are counterfeited from essential medicines to lifestyle drugs” at line 109. We included the suggested references in the revised version of the manuscript (reference 19, 61 and 62).

Some minor grammatical issues:
"Strength and Limitations" : "are a must" not "are must"; "Alli" is spelled wrong

Response: We corrected the above mentioned errors in the edited version of the manuscript.

Additional correction: We edited figures at lines 265 and 268 to avoid confusion that one sample (daidai hua) actually contained sibutramine, although it was marketed as supplement and herbal product (mentioned at line 273).

**VERSION 2 – REVIEW**

| | |
|---|---|
| **REVIEWER** | Timothy Ken Mackey, MAS<br>Senior Research Associate<br>Institute of Health Law Studies, California Western School of Law |
| **REVIEW RETURNED** | 25/03/2012 |

| | |
|---|---|
| **THE STUDY** | Needs further copyediting and clarification of language in the manuscript. |
| **RESULTS & CONCLUSIONS** | Again, piece needs further proofing/copyediting. |
| **GENERAL COMMENTS** | Thank you for your changes, some comments below:<br><br>-Methods:<br>>Not sure why whole methodology on ED drugs is mentioned, perhaps better to focus just on anti-obesity drugs? I think the discussion regarding ED drug availability on the identified sites<br>>A little unclear on this sentence: "Samples of the anti-obesity medicines were purchased from selected sites according to the smallest priority number found for a medicine that had not been purchased from a previous website" please clarify a bit.<br>>A little confused as in methods section it states that sites were screened out "provided they did not mention their physical address" but in the results section mentions that 15 out of the 36 sites did not show their physical address? Does this mean results include sites that were screened out and not screened out? Confused here.<br>Quality analysis: 30 results were excluded due to insufficient materials? How could have this impacted results?<br><br>This is an important topic, with important findings and a number of interesting data points and though the results don't have much power, they still warrant publication. I recommend this piece for publication, it just needs to be cleaned up and issues above need to be clarified as they are not well understood in the current language. |

**VERSION 2 – AUTHOR RESPONSE**

Responses on Reviewer’s Comments

Reviewer: Timothy Ken Mackey, MAS
Senior Research Associate

Institute of Health Law Studies, California Western School of Law

Needs further copyediting and clarification of language in the manuscript.
Thank you for your changes, some comments below:

-Methods:
>Not sure why whole methodology on ED drugs is mentioned, perhaps better to focus just on anti-obesity drugs? I think the discussion regarding ED drug availability on the identified sites

Response: Thanks so much for the comments.
Based on our previous experiences on online medicine studies (reference 5 and 35), it was presumed that websites offer counterfeit ED drugs may also offer other varieties of counterfeit medicines. We added new texts and our references at lines 136- 138 (pdf version) in this regard.

Since ED drugs were not targeted in this study, the information on ED drug availability on the identified sites was not retained sufficiently. The sites were identified from their advertisement of unrealistic strengths (e.g.: 50 and 100 mg of Cialis and Levitra) and colors of ED drugs reported in the cited reference 33, as mentioned at line 146 (pdf version).

>A little unclear on this sentence: "Samples of the anti-obesity medicines were purchased from selected sites according to the smallest priority number found for a medicine that had not been purchased from a previous website" please clarify a bit.

Response: We edited the text at lines 158 - 161 (pdf version) as “We purchased one anti-obesity medicine that was listed first in one of the selected sites. In subsequent selected web sites, we purchased another brand or product of anti-obesity medicines, which was listed first.”

>A little confused as in methods section it states that sites were screened out "provided they did not mention their physical address" but in the results section mentions that 15 out of the 36 sites did not show their physical address? Does this mean results include sites that were screened out and not screened out? Confused here.

Response: As mentioned in the methodology, the sampling sites were selected in five different steps. Among 36 selected sites, 15 sites were yielded from the 1st step of our search and these 15 sites did not mention any physical address. The presence or absence of physical addresses was not considered in the 2nd through 5th steps of our search. So, the other 21 sites resulted in 2nd - 5th steps of the Internet search. Two of these 21 sites did not also mention physical address in their sites. We edited texts at lines 237 - 243 for better clarification.

Quality analysis: 30 results were excluded due to insufficient materials? How could have this impacted results?

Response: These 30 samples were received in divided shipments mentioned at lines 246 - 247. For divided shipments we treated them as separate samples. We analyzed one of such kinds of identical samples consigned from a same source. Texts have been edited at lines 237 – 247 and 315 - 317 of pdf version. Since requested quantities of unit samples were divided, they lack sufficient quantity to analyze them all. Divided shipments might be considered as an important finding of our results.

Additionally we copyedited and truncated texts at lines 68, 86, 102, 107 - 116, 128 - 135, 169 - 173, 237, 293 - 294, 358, 367 and 409 - 415 (of pdf version).