PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Substandard and falsified medicines in the UK: A retrospective review of drug alerts (2001–2011)
AUTHORS	Almuzaini, Tariq; Sammons, Helen; Choonara, Imti

VERSION 1 - REVIEW

REVIEWER	Amir Attaran, University of Ottawa, Canada. No competing interests.
REVIEW RETURNED	02-Apr-2013

THE STUDY	This paper has a two methodological flaws, which unfortunately by their magnitude are fatal. First, the 1992 WHO definition of "counterfeit" medicine that the authors use is no longer supported by WHO as of 2011. The new term is "SSFFC" medicine, although that is rather a meaningless jumble. If one wants to use the old definition of "counterfeit", the reason for this should be clearly explained, which it is not. The authors are suggested to see WHO Fact Sheet 275 for further details of WHO's policy change, and more importantly, the WHA resolutions on the subject passed in 2010-2012. Second, even if one wanted to use the 1992 WHO definition of "counterfeit", here there is not enough data to do so. The WHO says that "counterfeit" medicines are "deliberately and fraudulently mislabelled with respect to identity and/or source." In this case, the authors (on page 5) note a number of medicine faults which define "substandard" medicines, but fail to explain how they delineate the unintentional faults from the deliberate and fraudulent faults. For example, if a medicine is found that contains the wrong active ingredient, by what criteria do the authors judge this an accidental error on the manufacturing line, or a deliberate fraud? They do not explain, and yet, the very essence of the distinction between substandard and falsified medicines lies is the deliberateness (or not) of the fault at hand.

REVIEWER	Maurizio Bonati, MD Head, Department of Public Health "Mario Negri" Research Institute Milan, Italy
REVIEW RETURNED	19-Apr-2013

RESULTS & CONCLUSIONS	The topic is of interest and scantly known. The presentation is a little unbalanced between the text and the tables. Text should be more analytical and tables and figures reduced. Fig.2, table 2 and 4 can be removed.

	Substandard and counterfeit medicines should be reported and discussed separately both in the text and in the tables: the causes and the preventive measures are different. Table 1: temozolomide is reported twice through "delivery issues". Table 3: verify the reported numbers Table 5: Atorvastatin 20mg 2006 twice. However, in the present form the Table is weak. A single and more informative Table for counterfeit medicines should be better. A discussion concerning the size of the two problems to the national use of drugs, the specific drugs involved as well as the manufactures should be of interest for the readers. A comparison between suspected risks reported in the issued alerts and pharmacovigilance reports could be discussed. References must be updated.

REVIEWER	Jillian Kohler, Associate Professor Leslie Dan Faculty of Pharmacy University of Toronto
REVIEW RETURNED	24-Apr-2013

THE STUDY	I found the paper to need more analysis in its arguments about falsified medicines. For example, the definition debates were mentioned but not discussed with much rigor and should be included in the body of the text. Also, very little is mentioned about the multisectoral nature of the problem, the global dimensions, the Internet etc. I would like the authors to provide more information about the context for the problem and also some of its health impacts. Is it a public health problem? A criminal problem? Both? Why?

VERSION 1 – AUTHOR RESPONSE

Reviewer: Amir Attaran,

This paper has two methodological flaws, which unfortunately by their magnitude are fatal.

Reviewer's comment: First, the 1992 WHO definition of "counterfeit" medicine that the authors use is no longer supported by WHO as of 2011. The new term is "SSFFC" medicine, although that is rather a meaningless jumble. If one wants to use the old definition of "counterfeit", the reason for this should be clearly explained, which it is not. The authors are suggested to see WHO Fact Sheet 275 for further details of WHO's policy change, and more importantly, the WHA resolutions on the subject passed in 2010-2012.

Authors' response: Thank you for your recommendation. We recognised this issue during our work and debated the definition to be used. We agree that the SSFFC definition is difficult to work with and so the 1992 definitions were considered clearer. Your paper debating around the new definition was also published as we were conducting our work. The 1992 WHO definition has been removed and we have referred to the new WHO definition and issues surrounding using it. The definitions worked to by the MHRA which are the ones that have been used to define the categories on their website have been clarified as below. We have changed the word counterfeit to falsified as we feel on consideration this is the better term, although both are used by the MHRA. We have added a paragraph in the methods section on page 4 describing the definitions used.

Reviewer's comment: Second, even if one wanted to use the 1992 WHO definition of "counterfeit",

here there is not enough data to do so. The WHO says that "counterfeit" medicines are "deliberately and fraudulently mislabelled with respect to identity and/or source." In this case, the authors (on page 5) note a number of medicine faults which define "substandard" medicines, but fail to explain how they delineate the unintentional faults from the deliberate and fraudulent faults. For example, if a medicine is found that contains the wrong active ingredient, by what criteria do the authors judge this an accidental error on the manufacturing line, or a deliberate fraud? They do not explain, and yet, the very essence of the distinction between substandard and falsified medicines lies is the deliberateness (or not) of the fault at hand.

Authors' response: We agree with the reviewer that data is needed to differentiate between falsified and substandard medicines. However we didn't attempt to define and classify the two problems but reported the conclusions of the investigations undertaken by MHRA. The delineation therefore has been made by the national authority, not by us, with the information available to them. We realise though that this was not mentioned clearly in the previous version and it is now added. We have also added the working definition used by the MHRA for falsified medicines. We have added a paragraph in the methods section on page 4 and also a paragraph at the end of the methods section on page7.

Reviewer: Maurizio Bonati, MD

Reviewer's comment: The topic is of interest and scantly known. The presentation is a little unbalanced between the text and the tables.Text should be more analytical and tables and figures reduced. Fig.2, table 2 and 4 can be removed.

Authors' response: Thanks for recommendation, Table 2 and 4 are now removed. However, we think that Fig 2 is more important as it describes the number of incidents over 11 years and shows their rising numbers. We have also significantly expanded the text and analysed the data more.

Reviewer's comment: Substandard and counterfeit medicines should be reported and discussed separately both in the text and in the tables: the causes and the preventive measures are different.

Authors' response: Falsified and substandard medicines are now separated in the text and in the tables, both in the results and discussion sections. Please see page no. 7-12.

Reviewer's comment: Table 1: temozolomide is reported twice through "delivery issues".

Authors' response: Temozolamide was recalled in two separate incidents. The MHRA issued two alerts for different batch numbers. We realise though that this was not mentioned and it is now stated in table 1.

Reviewer's comment: Table 3: verify the reported numbers.

Authors' response: We have checked the reported numbers and wish to confirm that they are correct.

Reviewer's comment: Table 5: Atorvastatin 20mg 2006 twice. However, in the present form the Table is weak. A single and more informative Table for counterfeit medicines should be better.

Authors' response: Atorvastatin was recalled in 2006 in two separate incidents with different batch numbers. The statement "Separate incidents of the same drug in the same year" is now added to the table.
As you recommended, we included all falsified information in one table.

Reviewer's comment: A discussion concerning the size of the two problems to the national use of drugs, the specific drugs involved as well as the manufactures should be of interest for the readers.

Authors' response: More data regarding the two problems in relation to the national use of the drugs, specific drugs used and manufacturers are added now in results section, Page no. 8-9. We also added online supplementary table (table 4) categorising substandard medicines by manufacturers and type of defects.

Reviewer's comment: A comparison between suspected risks reported in the issued alerts and pharmacovigilance reports could be discussed.

Authors' response: Information regarding the adverse events associated with defective medicines unfortunately is not in the public domain. We have recognised that this is a limitation of our study and added text to the limitations section on page 13.

Reviewer's comment: References must be updated.

Authors' response: The references are updated.

Reviewer: Jillian Kohler

Reviewer's comment: I found the paper to need more analysis in its arguments about falsified medicines. For example, the definition debates were mentioned but not discussed with much rigor and should be included in the body of the text.

Authors' response: Thank you for your recommendation. We have expanded the section on the different definitions of falsified medicines (see methods section, page 4).

Reviewer's comment: Also, very little is mentioned about the multisectoral nature of the problem, the global dimensions, the Internet etc.

Authors' response: We have expanded the discussion on falsified medicines (see discussion, page 11 and 12).

Reviewer's comment: I would like the authors to provide more information about the context for the problem and also some of its health impacts. Is it a public health problem? A criminal problem? Both? Why?

Authors' response: We have extended the discussion to mentioned these issues within the discussion on falsified medicines (see page 11 and 12).

VERSION 2 – REVIEW

REVIEWER	MAurizio Bonati, MD Head Department of Public Health Mrio Negri research Institute Via G: La Masa 19 no competing interest
REVIEW RETURNED	05-Jun-2013

GENERAL COMMENTS	The Authors adequately answered and replied to reviewer's

	questions and suggestions. Manuscript in the present form is improved.