PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	THE EFFECTIVENESS OF MEDICINE AUTHENTICATION TECHNOLOGY TO DETECT COUNTERFEIT, RECALLED AND EXPIRED MEDICINES: A TWO STAGE QUANTITATIVE SECONDARY CARE STUDY
AUTHORS	Naughton, Bernard; Roberts, Lindsey; Dopson, Sue; Chapman, Stephen; Brindley, David

VERSION 1 - REVIEW

REVIEWER	Abubakr Abdelraouf Alfadl Head, Department of Pharmacy Practice Unaizah College of Pharmacy Qssim University Unaizah, Qassim Saudi Arabia
REVIEW RETURNED	02-Sep-2016

GENERAL COMMENTS	GENERAL The subject of this paper discusses a topic with high importance in the domain of counterfeit medicines and the significance of similar studies is growing since drug counterfeiting is spreading worldwide. The major approaches of the study are acceptable, however, as noted in page 15, line 36 onward that there are 'concerns regarding the growing number of protocols and guidelines which require attention by NHS staff, which in this case may also have a part to play in non-compliance', this note intensifies my concern about the design and makes it more difficult for me to understand the logic behind the design identifying products as either 'Authenticated elsewhere' (counterfeit), 'Item Expired', 'Item Recalled (product or batch)' 'Authenticated' or 'Already Authenticated here'. This design further complicated and increased the need for attention to a protocol already complicated and suffering, because of that complication and need for attention, from non-compliance, while in reality authentication technologies do not make that differentiation, instead they only identify products as either authentic or non-authentic. SPECIFIC INTRODUCTION 1/ Defining 'Counterfeit Drugs' is an important step to talk about it because there is no universally agreed definition on this term and readers should be able to know which products your work is referring to. METHODS Sample Selection 1/ Page 5, line 10 give the full term the first time abbreviation mentioned ex. Falsified medicines directive (FMD), pharmacy supervised sale (P), and general sales list (GSL).

	RESULTS 1/ It is confusing to say that there are operational detection rate 1 (ODR1) and operational detection rate 2 (ODR2) which gives a misunderstanding of two different processes of operational detection while in fact there is only one operational detection calculated in two different ways. In what is called ODR1 medicines detected and quarantined were calculated out of the total labeled medicines included (48/92 and 47/88), and in what is called ODR2 the same number of medicines detected and quarantined were calculated out of medicines authenticated (48/59 and 47/54). It is better to delete ODR1 as it gives no added information, instead it promotes a misunderstanding that there is a statistically significant effect exerted by the operator detection (ODR) capacity, while actually the only statistical significant effect exerted by the operator authentication (OAR) capacity. 2/ Page 9, lines 14 and 15, it is better to label the box in figure 4 as operator authentication (OAR) instead of Database Detection because it is presented before that database detection is 100% , so it is not a factor to be presented and studied again. 3/ Page 11, it is better to present and comment on the results of OAR as it has the significant effect, not ODR. 4/ Page 12, line 7, the comment on Z tests seems true for ODR2 not ODR1, please check. DISCUSSION 1/ Page 13, line 11, it is stated that 'the data generated identified a gap between serialized medicines entered into the system and those identified by the authenticating technology, the operating authentication rate (OAR)'. From the data, there is no gap between serialized medicines entered into the system and those identified by the authenticating technology (database detection rate is 100%), but there is a significant difference between serialized medicines entered into the system and those screened or authenticated by the operators (OAR), so it is better the words 'identified by the authenticating technology' be replaced by 'screened or authenticated by operators'. 2/ Page 14, line 6, in line with the previous suggestion to drop ODR1, should be rewritten to be between overall group in terms of ODR compared to the expected legislative detection rate of 100%. 3/ Page 14, line 24, replace 'ODR1' by 'ODR (14/44)'. Further Research 1/ Page 16, line 3, detection rate is not less than optimum as results for ODR gave non-significant results.

REVIEWER	Klara Degardin Roche Switzerland
REVIEW RETURNED	07-Sep-2016

GENERAL COMMENTS	The paper is interesting and deals with a topical issue. To my knowledge it is new. Some points should thus be addressed: 1. p2 l49: was are the data points? please explain. 2. p3 l30: please detail the process better. There is first suspicion from the patients or the customs and then the lab analyses the samples. Please explain who could use this code in the routine. 3. p4 l16: please define better the parameters (OAR, TDR etc) and explain their utility. 4. p5 fig1: please explain the abbreviations.

	5. p6 l21: be careful with the use of counterfeit, falsified and copied. What is for you the difference? 6. p6 fig2: too small, cannot be read. 7. p8 l19: "no one person"? 8. p8 fig4: be careful with the display. Cannot be read. Also the figure is not clear. 9. p11 table 1: the results are not presented clearly. 10. p13 l11-18: do not understand the argumentation. Please present it more clearly. 11. p14 l47: "Study positives and negatives"? is that a display error? 12. A conclusion is missing.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name
Abubakr Abdelraouf Alfadl

Institution and Country
Head, Department of Pharmacy Practice
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Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below GENERAL the subject of this paper discusses a topic with high importance in the domain of counterfeit medicines and the significance of similar studies is growing since drug counterfeiting is spreading worldwide. The major approaches of the study are acceptable, however, as noted in page 15, line 36 onward that there are ‘concerns regarding the growing number of protocols and guidelines which require attention by NHS staff, which in this case may also have a part to play in non-compliance’, this note intensifies my concern about the design and makes it more difficult for me to understand the logic behind the design identifying products as either ‘Authenticated elsewhere’ (counterfeit), ‘Item Expired’, ‘Item Recalled (product or batch)’ ‘Authenticated’ or ‘Already Authenticated here’. This design further complicated and increased the need for attention to a protocol already complicated and suffering, because of that complication and need for attention, from non-compliance, while in reality authentication technologies do not make that differentiation, instead they only identify products as either authentic or non-authentic.

RESPONSE: The falsified medicines directive mandates the identification of counterfeit expired and recalled medicines, furthermore all authentication technologies in Europe must provide ‘blueprint service’ (a service which meets certain minimum requirements) which includes the identification of expired, recalled and counterfeit medicines as per European medicines verification organisation instruction. For this reason we tested not only the identification of counterfeit but also expired and recalled medicines.

SPECIFIC
INTRODUCTION
1/ Defining 'Counterfeit Drugs' is an important step to talk about it because there is no universally agreed definition on this term and readers should be able to know which products your work is

referring to.

RESPONSE: Agreed, the definition of a counterfeit drug and falsified drug has now been introduced to the introduction.

METHODS
Sample Selection
1/ Page 5, line 10 give the full term the first time abbreviation mentioned ex. Falsified medicines directive (FMD), pharmacy supervised sale (P), and general sales list (GSL).

RESPONSE: Agreed, this alteration has now been made.

RESULTS
1/ It is confusing to say that there are operational detection rate 1 (ODR1) and operational detection rate 2 (ODR2) which gives a misunderstanding of two different processes of operational detection while in fact there is only one operational detection calculated in two different ways. In what is called ODR1 medicines detected and quarantined were calculated out of the total labelled medicines included (48/92 and 47/88), and in what is called ODR2 the same number of medicines detected and quarantined were calculated out of medicines authenticated (48/59 and 47/54). It is better to delete ODR1 as it gives no added information, instead it promotes a misunderstanding that there is a statistically significant effect exerted by the operator detection (ODR) capacity, while actually the only statistical significant effect exerted by the operator authentication (OAR) capacity.

RESPONSE: The term ODR1 has been removed from his study and the abstract has been altered to reflect this. Instead a general reference has been made to explain that not all medicines entered into the study were scanned and subsequently quarantined. The only abbreviation referring to detection is now ODR (formally known as ODR2)

2/ Page 9, lines 14 and 15, it is better to label the box in figure 4 as operator authentication (OAR) instead of Database Detection because it is presented before that database detection is 100% , so it is not a factor to be presented and studied again.

RESPONSE: Agreed and completed.

3/ Page 11, it is better to present and comment on the results of OAR as it has the significant effect, not ODR.

RESPONSE: Agreed, more emphasis is put on OAR and the reference to the former ODR1 has been removed

4/ Page 12, line 7, the comment on Z tests seems true for ODR2 not ODR1, please check.

RESPONSE: Correct, that should have read ODR2 that must have been a typo. That now reads ODR as there is no longer an ODR1 and ODR2.

DISCUSSION
1/ Page 13, line 11, it is stated that ‘the data generated identified a gap between serialized medicines entered into the system and those identified by the authenticating technology, the operating authentication rate (OAR)’. From the data, there is no gap between serialized medicines entered into the system and those identified by the authenticating technology (database detection rate is 100%), but there is a significant difference between serialized medicines entered into the system and those

screened or authenticated by the operators (OAR), so it is better the words 'identified by the authenticating technology' be replaced by 'screened or authenticated by operators'.

RESPONSE: I agree that this is misleading and have changed this as per your recommendation.

2/ Page 14, line 6, in line with the previous suggestion to drop ODR1, should be rewritten to be between overall group in terms of ODR compared to the expected legislative detection rate of 100%.

RESPONSE: Agreed and changed

3/ Page 14, line 24, replace 'ODR1' by 'ODR (14/44)'.

RESPONSE: The abbreviation ODR1 has been removed throughout and only ODR remains

Further Research
1/ Page 16, line 3, detection rate is not less than optimum as results for ODR gave non-significant results.
RESPONSE: Agreed. That statement has been changed to 'for less than optimum authentication rates and less than absolute detection rates'

Reviewer: 2

Reviewer Name
Klara Degardin

Institution and Country
Roche Switzerland

Please state any competing interests or state 'None declared':
none declared

Please leave your comments for the authors below The paper is interesting and deals with a topical issue. To my knowledge it is new.
Some points should thus be addressed:
1. p2 l49: was are the data points? please explain.

RESPONSE: This has been changed to 'This study is based on the inclusion of 4,192 2D data matrices entered into a live hospital dispensary '

2. p3 l30: please detail the process better. There is first suspicion from the patients or the customs and then the lab analyses the samples. Please explain who could use this code in the routine.

RESPONSE: To clarify your point I have rewritten the sentence which now reads, 'The detection of counterfeit medicines by customs officials usually occurs as a result of intelligence or random checks, suspect medicines are then sent to a laboratory based analysis'

3. p4 l16: please define better the parameters (OAR, TDR etc) and explain their utility.

RESPONSE: These parameters are now explained in this section

4. p5 fig1: please explain the abbreviations.

RESPONSE: This change has been made in accordance to both reviewer comments

5. p6 l21: be careful with the use of counterfeit, falsified and copied. What is for you the difference?

RESPONSE: A clear description has now been made in the introduction as per both reviewer comments

6. p6 fig2: too small, cannot be read.

RESPONSE: Figure 2 and 3 have been made larger

7. p8 l19: "no one person"?

RESPONSE: This has been changed to 'Staff are not however permitted to be involved in both stages for the same prescription according to hospital policy'

8. p8 fig4: be careful with the display. Cannot be read. Also the figure is not clear.

RESPONSE: The figure has been enlarged and made clearer as per the request of both reviewers

9. p11 table 1: the results are not presented clearly.

RESPONSE: Changes have been made to make this figure clearer

10. p13 l11-18: do not understand the argumentation. Please present it more clearly.

RESPONSE: Agreed, now amended to state 'The OAR which represents user compliance across both stages was 66.3%. When compared to the expected standard of 100% this figure appears to be relatively low which may be due to operator compliance issues.

11. p14 l47: "Study positives and negatives"? is that a display error?

RESPONSE: Corrected. That heading are now in bold.

12. A conclusion is missing.

RESPONSE: Conclusion has now been added.

VERSION 2 – REVIEW

REVIEWER	Abubakr A. Alfadl Unaiazah College of Pharmacy Qassim University Saudi Arabia
REVIEW RETURNED	10-Oct-2016

GENERAL COMMENTS	All previous concerns have been well rectified and the manuscript is satisfactory.