PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A post hoc study to investigate the potential causes of poor quality of cardiovascular medicines collected in sub-Saharan countries
AUTHORS	Secretan, Philippe-Henri; Antignac, Marie; YAGOUBI, Najet; Bernard, Mélisande; PERIER, Marie Cécile; TAKOMBE, Jean Laurent; BALDE, Dadhi; N'GUETTA, Roland; IKAMA, Méo Stéphane; ZABSONRE, Patrice; SIDI ALY, Abdallahi; JOUVEN, Xavier; DO, Bernard

VERSION 1 – REVIEW

REVIEWER	Beata Sarecka-Hujar Medical University of Silesia in Katowice, School of Pharmacy with the Division of Laboratory Medicine, Poland
REVIEW RETURNED	13-May-2020

GENERAL COMMENTS	Dear Authors, I had an opportunity to review your manuscript. The topic is of scientific interests. However, there are some issue that should be addressed: 1. I understand that the current research follows previous analyses however in the present study you are analysing samples of two drugs, captopril and amlodipine, thus more information about the samples should be shown, i.e. number of brand name versions of captopril and number of amlodipine; similarly for generic versions; if some of the brand versions repeated in different countries involved you should state this. 2. Were any samples of amlodipine and captopril counterfeit? 3. Some kind of flow diagram regarding number of samples obtained in each country and in each place (licensed or unlicensed) would give clearer picture for the sample collection. 4. The description of statistical analyses should be separated as a new paragraph. 5. The comparisons regarding the place of obtaining samples and version of the sample should be made (i.e. licensed vs unlicensed; brand vs generic). 6. line 131-133 - those two sentences should be one 7. Limitations of the study are missing.

REVIEWER	Dr. Mercy Maina Moi Teaching and Referral Hospital Hospital, Kenya.
REVIEW RETURNED	17-Jul-2020

GENERAL COMMENTS	Introduction • Some phrases may require editing – English e.g. Thus, under the impulse of X. Jouven, ….. Methods:

	• Which method was used to ensure randomization of the "licensed" pharmacies? • Where there any measures taken to ensure the drugs did degrade while being sent from West Africa to the coordinating center in France? • Were the sources of the medications, licensed vs unlicensed, factored? The quality of packaging may be different dependent on the source • Authors only mention a coordinating center in center in France. Provide a description of the setting in which the analyses were conducted. Results: • Could you include a details on generic Vs brand for the samples that were analyzed • There is a discrepancy between the figures entered in Table 1 and the results description • There is a discrepancy in the results "the group with PVC blister 199 packaging (median=96.60, n=245). • Provide the full names for abbreviations in the figures Discussion • Can you include the country of origin for the low quality drugs? This is to determine / eliminate the question on whether it's storage practices within a specific country • The title included "uncontrolled circuits" yet the levels of control across the countries are not evaluated or discussed in the paper • Were the drugs still within the expiry period when the purity studies were conducted? • Section has errors in sentence construction that may be attributed to their length – shorter clearer sentences would be better

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name
Beata Sarecka-Hujar

Institution and Country
Medical University of Silesia in Katowice, School of Pharmacy with the Division of Laboratory Medicine, Poland

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

Please leave your comments for the authors below
Dear Authors,
I had an opportunity to review your manuscript. The topic is of scientific interests.
However, there are some issue that should be addressed:
1. I understand that the current research follows previous analyses however in the present study you are analysing samples of two drugs, captopril and amlodipine, thus more information about the samples should be shown, i.e. number of brand name versions of captopril and number of amlodipine; similarly for generic versions; if some of the brand versions repeated in different countries involved you should state this.
A new chapter: "3.1. Collected drug samples" including a description of the number of brand name versions of captopril and amlodipine along with the number of generic versions for the two drugs has

been added to the manuscript (lines 154-165).
“A total of 305 amlodipine and 235 captopril drug samples were collected in the ten countries. The amount of drug samples collected as a function of the countries and their place of purchase is summarized in Table 1. Overall, 150 of the 305 amlodipine and 140 of the 235 captopril drug samples considered in the study were obtained from licensed places of sale (Table 1). 265 and 195 drug samples were respectively identified as amlodipine and captopril generic drugs.”

2. Were any samples of amlodipine and captopril counterfeit?
The study was not designed with the aim to identify counterfeit drugs, but rather to get an insight into the quality of the products circulating. In that sense, we did not identify any drug samples that could be counterfeit.

3. Some kind of flow diagram regarding number of samples obtained in each country and in each place (licensed or unlicensed) would give clearer picture for the sample collection.
The new chapter: “3.1. Collected drug samples” includes a table summarizing the samples obtained in each country and in each place is proposed in the revised manuscript:
Table 1: number of collected amlodipine and captopril drug samples as a function of country and place of purchase (i.e. licensed or unlicensed). DRC democratic Republic of the Congo; NA: not applicable.

	Amlodipine			Captopril		
	Licensed	Unlicensed	Total	Licensed	Unlicensed	Total
Benin	20	30	50	20	30	50
Burkina Faso	10	NA	10	20	NA	20
Congo-Brassaville	NA	30	30	10	10	20
Côte d'Ivoire	30	45	75	30	15	45
DRC	20	NA	20	10	NA	10
Guinea	NA	10	10	NA	10	10
Mauritania	20	20	40	30	NA	30
Niger	30	NA	30	NA	10	10
Senegal	NA	20	20	NA	20	20
Togo	20	NA	20	20	NA	20
Total	150	155	305	140	95	235

4. The description of statistical analyses should be separated as a new paragraph.
The manuscript has been changed accordingly (line 146).

5. The comparisons regarding the place of obtaining samples and version of the sample should be made (i.e. licensed vs unlicensed; brand vs generic).
These data were already presented and discussed in our previous articles (Ref 6.: Antignac, M. et al. Fighting fake medicines: First quality evaluation of cardiac drugs in Africa. Int. J. Cardiol. 243, 523–528 (2017)).
The introduction has been changed accordingly for (lines 77-85):
“It was showed that branded drugs were less likely to be of poor quality compared to generic or medicines with unknown version ($p<0.001$) ; conversely place of sale was not significantly associated with the proportion of poor quality ($p = 0.29$)6. Examination of the identity and assay of the active substances in the various samples collected revealed that among the products tested, only those based on amlodipine and captopril had very low active substance content that could be less than 75% of those expected6. The observation that the biggest quality defects were highlighted and circumscribed around these two molecules motivated the team to search for additional information in particular regarding their stability.”

6. line 131-133 - those two sentences should be one
The manuscript has been changed accordingly (coma removed ; lines 141-143).

7. Limitations of the study are missing.
A section: « limitation of the study » has been added to the discussion section (lines 295-300) :
“4.1. Limitation of the study
This study is of an observational type and even if as much information as possible has been collected for the research and attribution of causes likely to be at the origin of the active substance dosage defect, other factors than those related to packaging and storage problems may be involved. The lack of active substance is most likely multi-factorial and it may be useful to explore with more samples when applicable.”----------

Reviewer: 2
Reviewer Name
Dr. Mercy Maina

Institution and Country
Moi Teaching and Referral Hospital Hospital, Kenya.

Please state any competing interests or state ‘None declared’:
None

Please leave your comments for the authors below
Introduction
• Some phrases may require editing – English e.g. Thus, under the impulse of X. Jouven, …..

Some parts of the sentences of the introduction have been edited accordingly:
« Thus, under the initiative of X. Jouven, »
« these two molecules motivated the team to search for additional information”

Methods:

• Which method was used to ensure randomization of the “licensed” pharmacies?

To clarify the choice of places of sale, we added the following sentences: « The pharmacies were randomly chosen from a list provided by the Council of the Order of Pharmacists of each country. Unlicensed markets were identified based on the local investigator's knowledge.” (lines 117-119).

• Where there any measures taken to ensure the drugs did degrade while being sent from West Africa to the coordinating center in France?
Yes, we used temperature recorders to ensure that the drugs did not undergo temperature excursions while being sent from West Africa to the coordinating center.

• Were the sources of the medications, licensed vs unlicensed, factored? The quality of packaging may be different dependent on the source
The impact of place of sale was already presented and discussed in our previous article (Ref 6.: Antignac, M. et al. Fighting fake medicines: First quality evaluation of cardiac drugs in Africa. Int. J. Cardiol. 243, 523–528 (2017)).
Moreover, the introduction has been changed for (lines 77-85):
“It was showed that branded drugs were less likely to be of poor quality compared to generic or

medicines with unknown version (p<0.001) ; conversely place of sale was not significantly associated with the proportion of poor quality (p = 0.29)6. Examination of the identity and assay of the active substances in the various samples collected revealed that among the products tested, only those based on amlodipine and captopril had very low active substance content that could be less than 75% of those expected6. The observation that the biggest quality defects were highlighted and circumscribed around these two molecules motivated the team to search for additional information in particular regarding their stability."

• Authors only mention a coordinating center in center in France. Provide a description of the setting in which the analyses were conducted.
We provided the missing information: « Chemical analyses of samples were blindly performed by the Department of Laboratories in Paris (AGEPS, AP-HP) » (lines 136-137).

Results:
• Could you include a details on generic Vs brand for the samples that were analyzed
A new chapter: "3.1. Collected drug samples" includes a description of the number of brand name versions of captopril and amlodipine along with the number of generic versions for the two drugs (lines 154-163).
"A total of 305 amlodipine and 235 captopril drug samples were collected in the ten countries. The amount of drug samples collected as a function of the countries and their place of purchase is summarized in Table 1. Overall, 150 of the 305 amlodipine and 140 of the 235 captopril drug samples considered in the study were obtained from licensed places of sale (Table 1). 265 and 195 drug samples were respectively identified as amlodipine and captopril generic drugs."

• There is a discrepancy between the figures entered in Table 1 and the results description
We fully agree with the reviewer recommendation. The discrepancies have been corrected in the table (table 2 in this new version of the manuscript). All the data provided through the text have been thoroughly double checked.
• There is a discrepancy in the results "the group with PVC blister 199 packaging (median=96.60, n=245).
The discrepancies have been corrected in the table 2. All the data provided have been thoroughly double checked.
• Provide the full names for abbreviations in the figures
The figures have been changed accordingly.

Discussion
• Can you include the country of origin for the low quality drugs? This is to determine / eliminate the question on whether it's storage practices within a specific country
These results have already been presented and discussed in another article we published (Antignac, M. et al. Quality Assessment of 7 Cardiovascular Drugs in 10 Sub-Saharan Countries: The SEVEN Study. JAMA Cardiol. 2, 223 (2017)) where it was showed that proportion of poor-quality drugs exceeded 20% in Benin, Congo Brazzaville, Niger, and the Democratic Republic of the Congo and was below 10% in Guinea, Senegal, and Togo.
However, based on our results, it is impossible to clearly state the main factor involved in the observed results i.e. "to determine / eliminate the question on whether it's storage practices within a specific country". Therefore, we have added a chapter limitation of the study (lines 295-300):
"4.1. Limitation of the study
This study is of an observational type and even if as much information as possible has been collected for the research and attribution of causes likely to be at the origin of the active substance dosage defect, other factors than those related to packaging and storage problems may be involved. The lack of active substance is most likely multi-factorial and it may be useful to explore with more samples when applicable."

• The title included “uncontrolled circuits” yet the levels of control across the countries are not evaluated or discussed in the paper
We fully agree with the reviewer recommendation. Accordingly, we changed the title of the manuscript for: «A post hoc study to investigate the potential causes of poor quality of cardiovascular medicines collected in sub-Saharan countries».

• Were the drugs still within the expiry period when the purity studies were conducted?
Indeed, the drugs were still within the expiry date when purity studies were conducted.

• Section has errors in sentence construction that may be attributed to their length – shorter clearer sentences would be better
Based on the reviewer suggestion, we have made shorter sentences in these parts of the text:
- Lines 275-277 :

« On the one hand, any dose lower than the dose to which the body has developed tolerance may induce an effect that is difficult to predict and may even be contrary to the action of the usual dose. On the other hand, the degradation products formed may be toxic. ».

VERSION 2 – REVIEW

REVIEWER	Beata Sarecka-Hujar Department of Basic Biomedical Science, Faculty of Pharmaceutical Sciences, Medical University of Silesia in Katowice
REVIEW RETURNED	15-Aug-2020

GENERAL COMMENTS	Thank for this revision. The mauscript was significantly improved. Congrats.

REVIEWER	Dr. Mercy Maina Moi Teaching and Referral Hospital, Kenya
REVIEW RETURNED	08-Sep-2020

GENERAL COMMENTS	You addressed the comments provided.