Author's response to reviews

Title: Microbiological contamination in counterfeit and unapproved drugs

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Author's response to reviews: see over
Dear Editor,

We submit the revised version of our manuscript.

The language of the manuscript has been improved with the help of our native English speaking colleague, Dr. Samantha Hewavitharana.

Additionally, we addressed all the reviewer’s comments and included them into the manuscript. Please find a detailed point-by-point response to the suggested improvements below.

We are looking forward to our response,

Yours sincerely,

Dieter Pullirsch

Reviewer 1:

Minor essential revisions:

1) discussion third paragraph. In the beginning of the paragraph a generalisation is made towards all counterfeit medicines. Although I can agree that the supposition is correct. It is not proven and therefore it is better to rewrite the sentence as: "it can be supposed..."

We agree with the reviewer’s opinion and have rewritten this paragraph.

Discretionary revisions

1) I think a remark should be made about a special group of "unapproved medicines". Some medicines are legal in the country of origin, since these countries do not recognise US and European
patent laws. Example of this is (the genuine) Kamagra. Often these products respond to high quality norms.

*It is true that this special group exists. We included this remark in the introduction. However, also for unapproved medicines that are legal in the country of origin a lot of falsifications are sold via the internet ("counterfeits of unapproved products") and we might not know their true origin.*

**Reviewer 2:**

The Title of this paper should be easily understood, while accurately reflecting its contents. The following changes may be considered - "illegal medicines" replaced by "counterfeit and unapproved drugs" and "increased microbiological burden" by "microbiological contamination".

*We appreciate this suggestion. For clarification, we have changed the title accordingly.*

As counterfeit and unapproved drugs were the main focus of this study, less specific term (illegal medicines) should be avoided. Confusion caused by inconsistencies in the use of these terms throughout the paper was unnecessary. It should be clear right at the beginning that this would address both counterfeit and unapproved drugs. It was disappointing that unapproved drugs were not mentioned until Material and Methods section.

*We have revised the article and tried to remove less specific terms. Whenever it was not possible to avoid a less specific term, we re-defined the term in brackets. We have included unapproved drugs now already in the introduction.*

All statements should be supported by references.

*We have included additional references. Now all statements are substantiated with references.*

More updated references should be quoted. References should be quoted accurately (ref 3).

*The references were updated and ref. 3 was corrected.*

The method of sampling of counterfeit and unapproved drugs for the present study based on the lots that were confiscated should be mentioned.
The method of sampling was inserted into the Material and Methods section. For illegal products a “lot” or “batch” definition does not really exist (e.g. we observe samples with identical batch numbers but different expiry date; different producers use the same template for packaging, e.g. pictures from the internet).

One herbal product was included in the study. Did this product contain herbs?

In the last paragraph of the result section we have included that the product contained brown, tried plant tissue.

Although this study focused on microbiological contamination, there should be some measurements of the drug contents. Such information, if available, would provide a more complete picture about the quality problems and health hazards caused by these drugs.

Measurements of the drug content were performed for most counterfeit samples. We have included a paragraph in the results section. Because this study focused on microbiological contamination, detailed information was included as an additional file. As seen in previous studies, main problems with illegal medicines are low levels of active pharmaceutical ingredients and unlabeled ingredients.

It would be useful to provide objective guidance on interpretations and implications of the microbiological findings. In particular, how serious was the health hazard to patients in general and immunocompromised subjects.

Total microbiological count is considered as a surrogate marker for proper hygienic conditions. Only limited numbers of samples were tested in our studies and in comparison, the illegal market seems tremendous. We have included in the text based on the observed pathogens and the observed concentrations of pathogens human infections seem unlikely for healthy people for the tested samples. However, the increased amount of cultivable microbiological organisms clearly indicates avoidable contamination. Whenever the hygienic conditions of production are insufficient the risk for detection of more serious pathogens increases with the number of tested samples. Therefore, a more detailed guidance based on the tested samples might not be useful.