Reviewer's report

Title: Accessibility and Potency of Uterotonic Drugs purchased by Simulated Clients in Four Districts in India

Version: 2 Date: 18 July 2014

Reviewer: Richard Lowe

Reviewer's report:

Review of:
Accessibility and Potency of Uterotonic Drugs purchased by Simulated Clients in Four Districts in India
Cynthia Stanton, Deepak Nitya Nand, Alissa Koski, Ellie Mirzabagi, Steve Brooke, Breanne Grady and Luke C Mullany
BMC Pregnancy and Childbirth (Submitted: 2014-03-02)

GENERAL COMMENTS
Overall, this is a very useful addition to the scientific literature on the issue of quality of maternal health medicines. Although there have been studies on the quality of oxytocin over time in the field, this is the first to estimate the rate of degradation of products in the field. The study provides useful supportive evidence of the contribution of this factor to general problem of oxytocin quality and some reassurance that products sampled were unlikely to be fake and likely were of sufficient potency when leaving the manufacturer.

I would suggest that the authors check the statistics in Tables 2 and 3. Also, it would be helpful to clarify the drug potency results section as some of the descriptions of the results and the content of Tables 4 and 5 is a little confusing. Other discretionary revisions relate to additional information that might be included if available. Minor essential revisions are mostly related to language.

MAJOR COMPULSORY REVISIONS
1. In the methods section, could the authors please state the statistical program and method used to calculate the percentages and exact binomial confidence intervals for the study.

While not an expert in statistics, I am concerned that there might be some inconsistencies in the data. Using an epitools calculator, calculating the estimate and exact binomial confidence interval using the Clopper Pearson method gives the same values for UP as appear in Table 2, but different values for Karnataka than those in Table 2.

The same epitools program and method gives the same values for UP and Karnataka as appear in Table 3.
Could the authors please re-check the analysis and confirm that the data in the tables is correct.

MINOR ESSENTIAL REVISIONS

1. Line 13. Lifesaving should be written as “Life-Saving”
2. Line 22. Include the word “drugs” after “anti-tuberculosis”
3. Line 69. Please include a reference to Concept Foundation study if possible
4. Line 113. Can the authors please clarify what the 90% and 50% refer to – is it the true proportion of oxytocin and ergometrine samples that are within API bounds?
5. Line 115. Please replace “multiple” with “two”. The study methods clearly describe that two ampoules are purchased, and using “multiple” could confuse as it could imply that more than two were purchased.
6. Line 206 and 207. For Tables 2 and 3, please add a legend to explain the P and N in each column.

DISCRETIONARY REVISIONS

1. Line 23 -25
   • Suggest rewriting this sentence to capture the requirement that drugs must be manufactured to specific standards AND undergo monitoring for quality at different points in the supply chain. They are two separate and important issues. Monitoring alone is not sufficient if the drugs have not been made to a sufficient standard.
   • Global fund does not just operate in low-income countries. Suggest removing “low-income”
   • Product quality monitoring is always mandated for Global Fund procurement. Manuscript states “often”

2. Line 53. Did the authors consider including the USP study conducted in Ghana in 2012 as part of the background review. The findings are available online. http://www.usp.org/sites/default/files/usp_pdf/EN/PQM/ghana-mch_mqm_report_final-mar_27_2013_rdct.pdf


4. Drug Potency section – Lines 209-255
   Some of this section is confusing and difficult to understand.
   • Lines 212-216. It’s not clear why the number of successful purchases in Karnataka led to the decision to test all ampoules from these districts. Was it
because the number of purchases was considered low or high? Please clarify.

Table 4 is confusing. The first column heading says “Analysis units” under which are two columns for 1 ampoule and 2 ampoules. However, the study design requires that two ampoules per pharmacy constitutes an analysis unit. Please check and correct if necessary.

Table 2 shows that 24 purchases of oxytocin were made in Bagalkot. Table 4 shows that there were 48 1 ampoule purchases recorded in Table 4, Table 5 also shows this (for the number of samples tested)? Were two ampoules purchased in each pharmacy? If so, then please correct Table 4 as this creates confusion about the procurement and analysis numbers.

If Table 4 is correct, then in Bagalkot and Hassan, it was possible to purchase 1 full analysis unit (2 ampoules) in each pharmacy, whereas in Agra and Gorakhpur, some of the purchases were only of 1 ampoule, as the text outlines? Please check the text in this section and Table 4 for accuracy and clarity.

- Line 222. The statement “Thus, ampoules that were out of specification did not tend to be far from manufacturer limits” needs some consideration. Some of the ampoules tested were a long way from manufacturer specifications. The important finding is that these products are out of specification, regardless of how close to manufacturer specification they are.

- Line 223-224. While the median is correct to use for what appears to be a skewed distribution, I’m not sure that it really tells you much about the range of product potency. Of more concern is the fact that even though the median is around 100%, 35% of samples are out of range. I might also be concerned that the sentence could be interpreted as “on average, there is sufficient drug in the samples products”.

- Line 238. 46 pharmacy pairs are described here, but Table 4 seems to show that only 1 ampoule from each pharmacy was collected. If this is the case, how can there be pairs of ampoules from each pharmacy? Please clarify this point and Table 4.

- Line 249. Did the study record storage conditions on the label for each of the samples and if so, whether the authors considered describing these conditions in the manuscript. This might help to explain the conditions of storage in pharmacies and whether it was according to manufacturer instructions or not.

- Line 272-273. It’s not clear why the description of the proportion of drugs with API less than 50% is included here. The previous sentence states that 96%-100% of samples are out of specification and it should not matter whether they are just out of, or a long way out of specification.

- Line 293. Suggest using the term “potency” instead of quality. Using ”potency” more accurately describes what has been measured in the study. “Quality” can also refer to other facets that include manufacturing.

- Line 296. Regarding the differences in potency between states, could this have
been due to different ages of drugs in each state – those in Karnataka were older than in UP? Did the authors consider exploring this in the analysis?

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests