Reviewer's report

Title: Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: a systematic review of the world literature

Version: 0 Date: 15 Dec 2015

Reviewer: Nigel Rawson

Reviewer's report:

This article is much improved but I still have concerns (see points 6 to 8 below). Some assumptions are still being made that are difficult to justify.

1. The authors now provide a definition of what they considered to be a medicinal product.

2. The authors use many sources to collect their information and provide information about them, although I am still not clear as to how they verified the accuracy of their data. Some of the errors that I noted in their e-appendix table 1 have now been corrected.

3. Only 1% of the products have the year of first ADR missing. This is good to see but somewhat disconcerting that they were not in the original submission.

4. Only one product in e-appendix table 1 (chlorphentermine) now has a year of first withdrawal preceding the year of first ADR report. This should be corrected.

5. I am pleased to note that the authors now try to set the risks within the context of the large number of successful products that have been approved.

6. While the authors acknowledge that they do not have information on the countries in which each drug was approved, I continue to believe that this is a major flaw. For example, the authors report in e-appendix Table 1 that acetarsol was withdrawn in Mauritius for hematologic reasons. The fact that it was withdrawn in Mauritius obviously means that it was approved for marketing in Mauritius. However, was the drug only approved in Mauritius? If so, was this due to the indications being particularly applicable to the Mauritius population, were applications not made elsewhere, or were they made and not approved? If applications were made elsewhere and consistently rejected, I would argue that the agencies are generally consistent and the Mauritius agency was aberrant. Therefore, based on data that do not include approval information, one cannot assess whether the agencies are consistent or not.

7. While drug safety risks have occurred for centuries, they were until the 20th century mainly due to a lack of knowledge. In the 20th century, the many drug discoveries were dramatic and healthcare providers, patients and governments were so impressed by the scientific advances that adverse drug reactions were frequently considered to be heavily outweighed by the benefits of the new drugs. Drug regulations were introduced in the 1930s to 1950s, but they had limited impact. I continue to argue that the real regulatory changes began as a result of thalidomide and still believe that the sub-analyses
should consist of products launched from 1960 onwards, even if it is not consistent with the authors' earlier work.

8. The authors conclude that "withdrawal of products following suspected adverse reactions, sufficiently serious to warrant withdrawal, has not improved consistently over the last 60 years." While it may not be consistent, there has certainly been improvement post-thalidomide, as their Figure 5 shows, especially after 1985 where 81% of the withdrawn products were discontinued within 5 years of the first ADR report. I think this should be acknowledged, together with the fact that their data do not allow any understanding of how many patients were impacted by the ADRs, which is most important.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Unable to assess

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No

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