PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	An Investigation into Drug Products Withdrawn from the EU Market between 2002 and 2011 for Safety Reasons and the Evidence Used to Support the Decision Making
AUTHORS	McNaughton, Rhian; Huet, Gwenaël; Shakir, Saad

VERSION 1 - REVIEW

REVIEWER	Maurizio Bonati, MD Head, Department of Public Health
REVIEW RETURNED	30-Oct-2013

GENERAL COMMENTS	The objective of the study of exploring the level of evidence used to support the withdrawal of marketing authorisation of drugs in the EU is interesting and relevant both to reflect on past procedures and give directions for future. However, in the present form the findings disappoint a bit expectations. The improvement of the level of evidence during the last ten years in the drug area is widely documented and recognized, even in pharmacovigilance. As reported by the authors, even the withdrawal from the market of drugs for safety reasons, it is increasingly based on high levels of evidence. So the main message of the study is a bit 'weak and poorly innovative. About exploring, it would be helpful to understand how and how much they contributed in the final decision evidence of the high level vs case reports. What is the contribution of the side effects reported in animal studies, case-control, cohort RCTs and meta-analysis vs. case reports analyzing single drug histories. It would be interesting to reflect on different national vs. centralized decisions vs. the same evidence with the same available evidence. A few examples are cited but not analyzed. Minor comments: The average time to withdrawal should be reported as median. Table 1 may be omitted. Table 2 should have a reading order not based on the alphabetical order of drugs but for class or adverse reaction or ... according to the importance that the authors want to give the presentation.

REVIEWER	Keith Hoffman AdverseEvents, Inc. USA
REVIEW RETURNED	05-Nov-2013

GENERAL COMMENTS	I think this paper is worthy of publication and adds to the field.

	Small comments: Abstract/"results" = I'd prefer to see the results listed as 4/19 for case-controlled studies, 4/19 for cohort studies, 12/19 for RCTs, and 5/19 for meta-analysis rather than have those four combined into "12/19." Lines 48-49 & 53-54, page 4 = Again, might it be more informative to list such past results in their individual categories, rather than as a combined result? Line 25, page 5 = Can the authors disclose the number of drugs that were omitted because of this inclusion criteria? Line 28, page 5 = I'd suggest that the authors may want to add more detail on how they identified scientific evidence as causative to withdrawal decisions. Table 4 = While the case count totals are interesting, did the authors consider performing a disproportionality analysis, or a related measure, on these drugs? Can they obtain the needed data to execute such calculations from Eudravigilance?

VERSION 1 – AUTHOR RESPONSE

To Maurizio Bonati,

Your thoughts on our manuscript are much appreciated.

The EMA publish a high level assessment report on their website detailing the risks associated with the drug in question following the decision to withdraw its marketing authorisation. As an example, here is the report published on the withdrawal of acomplia (rimonabant) e.g. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500014774.pdf. Without the detailed minutes or opinions of the CHMP, it is difficult to ascertain how the evidence cited was weighted in the decision making.

Due to time constraints, we were unable to ascertain why drugs were withdrawn in some countries but not in others. As we mention in the manuscript, it was difficult to obtain information about certain drugs due to language limitations in understanding national websites, the unavailability of key information and the transparency of the decision making.

We have addressed all of your minor comments below:
1. The median length of time to withdrawal has now been included to replace the mean e.g. The average time to withdrawal was 23 years with an interquartile range (IQR) of between 4 and 46 (Table 1).
2. Table 1 has been removed from the manuscript.

3. Table 2 has been renamed as Table 1 and re-ordered to group ADRs together i.e. all drugs withdrawn from the market due to hepatoxicity safety concerns e.g. Nefazodone, Ximelagatran / Melagatran, Lumiracoxib and Sitaxentan are listed chronologically.

To Keith Hoffman,

Thank you for deeming this paper worthy of publication. We have addressed your small comments below:

1. The results have been separated as per your suggestion.

2. Again, the results have been separated as per your suggestion.

3. Unfortunately, we did not record the number of drugs that had restrictions or the marketing authorisation of one particular dosage form/dose/indication withdrawn during the course of the research and so therefore this information is not available.

4. More detail has been included in line 28, Page 5: The scientific evidence leading to the withdrawal decision was identified from a search within PubMed, the EMA website (published documents searched included: “Press releases”, “Questions and Answers” and “Scientific conclusions”) and national medicines agencies websites. Within the “Questions and Answers” reports and “Press releases”, prepared by the EMA, a summary of the reviewed evidence with reference to study type (e.g. RCT, animal study) is often included.

5. We agree with the reviewer that the number of reported events to Eudravigilance is a crude measure. However, calculating disproportionality figures will not add value to our work. The reason is that disporportionality is itself a crude method for signal detection, not for signal assessment and evaluation as would have been the case when the risk/benefit decisions were made for the withdrawal of these products. Moreover, the disproportionality method it is not suitable for all the types of events leading to the product withdrawals, such as events with high background incidence in the underlying population.