PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Post-marketing studies for novel drugs approved by both the FDA and EMA between 2005 and 2010: a cross-sectional study
AUTHORS	Zeitoun, Jean-David; Ross, Joseph; Atal, Ignacio; Vivot, Alexandre; Downing, Nicholas; Baron, Gabriel; Ravaud, Philippe

VERSION 1 – REVIEW

REVIEWER	Enrique Seoane-Vazquez Chapman University School of Pharmacy, US
REVIEW RETURNED	04-Aug-2017

GENERAL COMMENTS	This is an interesting area of research. The methodology used in the study limits the interpretation and applicability of the results. Introduction The introduction should describe the FDA and EMA postmarketing regulations and policies. Objectives [Page 6. Lines 8-12]: “They [FDA and EMA] tend to maintain similar premarket regulatory standards, and drug manufacturers likely submit the same evidence to both as part of the premarket application process.” Previous studies have found substantial differences in pre-market regulatory standards (e.g. generic designations, accelerated approvals). Also, include a reference supporting that drug manufacturers submit the same evidence to both regulatory agencies. [Page 7, Lines 22-24] “ We also sought to examine differences between the initial label and the specific clinical condition studied in the post-marketing trials. “. The concept of “clinical condition” is not defined or use in the study. Clarify if the clinical condition is the disease or health problem described in the indication sections of the label. Methods The study used a definition of post-marketing that departs from the definition used by the FDA and the EMA. The FDA and the EMA consider post-marketing trials those conducted after approval. The authors use a different definition: “…all trials whose starting date had preceded the first regulatory submission (to the FDA or EMA) by 1 year or less.” This difference in definitions makes it difficult to interpret the findings of the study considering other studies and publicly available reports. The authors could consider to redo the study using the standard definition of post-marketing trial. The study should differentiate studies done by the sponsor or marketing authorization holder company or companies. These include post-marketing studies required by the regulatory agencies to the sponsor company.

	The study does not explain how the indication was defined and compared. Previous studies found significant differences in indications for the same drugs approved by the EMA and the FDA. The study does not explain how the study accounted for drugs with different indication approved by the EMA and the FDA. The study does not account for lags in drug approval between the FDA and the EMA. Some trials may be pre-marketing in one agency and post-marketing in the other due to the approval lag. Explain how the study accounted for cases where the orphan status was granted to only some of the indications approved for a drug. The study should differentiate clinical trials for drugs approved under accelerated approval processes. Drugs approved under accelerated programs have heavier post-marketing requirements. [Page 7, Lines 22-24] “Studies of generic drugs, reformulations, combination therapies and non-therapeutic agents such as radiographic dye were not included.” Clarify what you mean by “studies of generic drugs.” [Page 8, Lines 11-12] “Anatomical Therapeutic Chemical code”. The ATC is not a code but a classification system. Figures It is difficult to interpret the information contained in the figures due to the large range of values represented (e.g. enrollment from 1 to 900K patients). The authors could present the information in tables.

REVIEWER	Rita Banzi IRCCS-Mario Negri Institute for Pharmacological Research, Italy I know some of the authors but currently I don't have active collaborations with them
REVIEW RETURNED	22-Aug-2017

GENERAL COMMENTS	General comment: I would like to thank the BMJ Open for giving me the opportunity to review this paper. My congratulations to the authors as this analysis seems to derive from a huge work. The collection of evidence on the physio-pathology of post-marketing research is of utmost importance. Nowadays, as early approvals are increasingly tempting several regulators, it is fundamental. We should gather evidence on the ability of post-marketing research to fill the knowledge gaps at the time of approval, expand the use to different population, or optimize schedules and algorithm of treatment. It would be very important also the assessment of post-marketing research values (less artificial conditions? more pragmatic?) and its real and alleged limitations. The paper by Zeitoun and colleagues provides a “comprehensive description of post-marketing trials registered in ClinicalTrials.gov, for a sample of drugs approved by both the FDA and EMA from 2005 to 2010.” The authors provide a very broad picture (median values and aggregate figures) that gives an overall idea on the trends and status of post marketing research. The applied methodology seems to be adequate and robust and the limitations linked to the use of one single (imperfect) register duly mentioned. Some interesting findings are presented, such as that almost 40% of the trials test drugs in indications other than those approved and the time pattern of trial inception after the first approval.

	Other aggregate findings are less meaningful: for example, the variability in number of trials or participants is probably a consequence of the large heterogeneity of the sample (from sorafenib to drugs for very rare diseases). Unfortunately, this data does not allow any conclusion on the usefulness of this post-market research to patients and health care systems. In other words, if it is done to address real medical needs, commercial reasons, academic pressures or other goals. Of course, this is far beyond the aim of the submitted paper and would be possible only considering specific therapeutic areas. My opinion is that the analysis could be of interest to the general readers of BMJ Open. However, some minor revisions could help to clarify some aspects of the manuscript. Specific comments Introduction The authors list some reasons for conducting post-marketing trials (page 6, line 29-47). I would suggest to include also the studies designed to target product sampling towards selected prescribers or users, the so-called seeding trials. I think these studies represent a big issue in post-marketing research. Maybe, seeding trials can be also touched in the discussion. The objectives section should better match the different aspects covered in the results section. It is clear that the first aim is the description of the post-marketing studies on the drugs included in the sample. It is now stated that the paper aims to explore differences between the initial label and the specific clinical condition studied in the post-marketing trials. However, there are several other analyses in the paper, as the influence of study sponsor (industry/non industry) and the analysis of the FDA supplemental indication, that should be reflected in the objectives. The analysis of the FDA supplemental indication sounds a bit out of the scope of the paper because it focuses on granted not just "explored" supplemental indications. I guess, that was not planned from the beginning. Methods Although based on (inevitable) arbitrary decisions (i.e. definition of post-marketing studies, leading drugs, etc.) the applied methods seems to be adequate and well described. It would be useful to add some clarification on how the categories "acute, intermediate and chronic treatment" were defined (see comment in the results section below). Results 1) Table 1 reports the characteristics of the 69 drugs included in the sample. It includes the number of drugs that have been approved on the basis of at least one active-controlled trial, placebo or no comparator as well as the number of patients in pivotal studies. Though interesting, the relevance of this info for the current analysis in unclear. Moreover this seems to be a finding of a previous analysis (ref 16); if so, it should be referenced. 2) Table 1 also reports the proportion of drugs to be used for acute, intermediate and chronic treatment. In the methods section, I was not able to find how these categories were defined. 3) While Figures are extremely clear and useful to understand the details on each of the included drugs, Table 2 is a bit unclear. Instead of having two separate column for industry and non-industry studies, I would suggest to report the data in lines, first all studies, then split in industry and non-industry (sometimes both industry/non industry data is not even needed as can be simply derived by subtraction).

	4) The proportion of randomized/observational post marketing trials could be reported also in the abstract. Discussion It would be useful to add some references when similar (but limited) analyses are mentioned (for instance page 15, lines 40-43) It should be acknowledged that this paper did not assess the relevance and usefulness of the clinical research done post-market. If I understand correctly, the study period for the trial sample is “up to 10 years” rather than nearly 10 years (page 15, lines 43-46) Other comments I found some discrepancies in the list of supplemental files order and numbering. At page 11 the “PRISMA” flowchart is cited as supplemental file S1 while it is named Figure 1 at page 32. However, Figure 1 is actually “Number of post-marketing trials and respective proportion of industry and nonindustry” I would suggest using “study” rather than “trial” along the document as both interventional and observational studies are included in the sample. If pre-approval studies are pivotal trials, I would suggest clarifying it. Rita Banzi, Mario Negri Institute for Pharmacological Research, 21 August 2017

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Enrique Seoane-Vazquez
Institution and Country: Chapman University School of Pharmacy, US
Competing Interests: None declared.

Comment 1: This is an interesting area of research. The methodology used in the study limits the interpretation and applicability of the results.

Response: We thank Reviewer#1 for the time taken to review our paper and for his interest.

Comment 2: Introduction
The introduction should describe the FDA and EMA postmarketing regulations and policies.

Response: We further explained post-marketing practices of both regulators in the Intro, and the revised text now states: “Drug evaluation continues after regulatory approval, in particular through post-authorization requirements and commitments. The US FDA can use several regulatory instruments and harness various sources for postmarketing evaluation of approved drugs. Among them are the FDA Adverse Reporting System and the Sentinel System [Ball R, CP&T 2016]. The EMA also has a set of post-authorization measures, from direct request by its dedicated committee, to specific obligations for certain drugs, all aiming at retrieving data for post-marketing assessment [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000037.jsp].”.

Comment 3: Objectives
[Page 6. Lines 8-12]: “They [FDA and EMA] tend to maintain similar premarket regulatory standards, and drug manufacturers likely submit the same evidence to both as part of the premarket application process.” Previous studies have found substantial differences in pre-market regulatory standards (e.g. generic designations, accelerated approvals). Also, include a reference supporting that drug manufacturers submit the same evidence to both regulatory agencies.

Response: We acknowledge that data comparing premarket evidence submitted to both leading regulators are lacking and we believed that anecdotally, they were highly similar. However, our phrasing might have been inadequate and we changed it so that the revised version now states: “They tend to maintain similar premarket regulatory standards, and drug manufacturers probably tend to likely submit the same evidence to both as part of the premarket application process, even though we lack comparative data.”.

Comment 4: [Page 7, Lines 22-24] “We also sought to examine differences between the initial label and the specific clinical condition studied in the post-marketing trials. “. The concept of “clinical condition” is not defined or use in the study. Clarify if the clinical condition is the disease or health problem described in the indication sections of the label.

Response: Clinical condition was retrieved from the regulatory label for each drug of the study sample. It was fully rewritten in a working paper that we add in the resubmission as an Appendix. However, for the sake of analysis, it was also classified according to the ICD-10 as stated in the manuscript so as to structure data in a homogeneous manner.
However, conditions studied in post-marketing trials were “manually” classified by the first author of the article, again according to the ICD-10, which is thought to be a classification of reference.
So as to clarify our research objectives, we rephrased it so that the revised text now states: “We also sought to examine differences between the condition of the initial label and the specific clinical condition studied in the post-marketing trials, […]”.

Comment 5: Methods
The study used a definition of post-marketing that departs from the definition used by the FDA and the EMA. The FDA and the EMA consider post-marketing trials those conducted after approval. The authors use a different definition: “…all trials whose starting date had preceded the first regulatory submission (to the FDA or EMA) by 1 year or less.” This difference in definitions makes it difficult to interpret the findings of the study considering other studies and publicly available reports. The authors could consider to redo the study using the standard definition of post-marketing trial.

Response: To our knowledge, there is no commonly agreed definition of post-marketing trials. Literally and therefore theoretically, post-marketing trials are those that are launched just after the granting of a marketing approval by any regulator. However, when doing the primary analysis of collected data, we realized that in practice, the launch of clinical trials followed a continuous pattern from very early phase I trials to late post-marketing observational studies. Put another way, we found that the pace of launch of clinical trials does not slow after completion of pivotal efficacy trials and therefore that trials are designed and launched between the completion of pivotal trials and the effective marketing authorization (i.e., during the regulatory submission and decision phases). Therefore, the distinction between premarket and post-marketing studies is not straightforward and somewhat artificial. That said, we decided that some trials launched after pivotal efficacy trials completion yet before official marketing approval should be considered post-marketing trials, in particular because in general, pharmaceutical companies are quite confident in the fact that marketing approval will be obtained and because those trials seek objectives that resemble those usually pursued by post-marketing studies.

As explained in the Methods, we therefore put a threshold at 1 year before the earlier regulatory submission to differentiate between preapproval studies and post-marketing trials. This is clearly debatable, yet we believe it is a relevant choice from a public health perspective. Last, there were only 236 trials (3.5% of the final sample) for which start date was prior to earlier marketing approval and that we included because we judged that they should be considered as post-marketing trials.

Comment 6: The study should differentiate studies done by the sponsor or marketing authorization holder company or companies. These include post-marketing studies required by the regulatory agencies to the sponsor company.

Response: We acknowledge that whether any given trial is sponsored by the marketing authorization holder (MAH) of the drug is paramount. In our study, we differentiated between industry-sponsored and non-industry-sponsored trials. Table 2 and several figures display the distinction. However, establishing for each of the 6679 post-marketing trials if the sponsor is the MAH of one of the studied drugs was out of the scope of our research and seems unfeasible at this stage. Similarly, screening each trial to determine whether it was required by any regulator after approval is unfeasible within a short time frame.

Comment 7: The study does not explain how the indication was defined and compared. Previous studies found significant differences in indications for the same drugs approved by the EMA and the FDA. The study does not explain how the study accounted for drugs with different indication approved by the EMA and the FDA.

Response: Some elements of response can be found above in the response to comment #4. Indications of initial labels and of clinical trials were manually reviewed by the 1st author and classified according to the same ICD-10. All processes are now transparently displayed in an added document embedded in the submission. In case of differences between FDA and EMA initial labels, all conditions were considered to belong to the originally approved indication. This is stated in the Methods, as ascertained by the following sentence of the manuscript: “When the initial label differed between the FDA and EMA, we accepted both labels as defining the originally approved indication. One of us (JDZ) performed this classification after careful review of each primary label.”

Comment 8: The study does not account for lags in drug approval between the FDA and the EMA. Some trials may be pre-marketing in one agency and post-marketing in the other due to the approval lag.

Response: Indeed, this is the case. As explained in the response to comment #5, we chose the earlier regulatory submission and then placed the cut-off at 1 year before so as to define a threshold for “post-marketing” trials.

Comment 9: Explain how the study accounted for cases where the orphan status was granted to only some of the indications approved for a drug.

Response: Actually, our analysis revealed that for each initial label, if an orphan status (or designation for the EMA) was granted, it was only for one condition. We did not study whether subsequent supplementary indications were also under an orphan status or not.

Comment 10: The study should differentiate clinical trials for drugs approved under accelerated approval processes. Drugs approved under accelerated programs have heavier post-marketing requirements.

Response: Following this comment from Reviewer #1, we retrieved data regarding accelerated approval and added it in our description (see Table 1, highlighted).

Comment 11: [Page 7, Lines 22-24] “Studies of generic drugs, reformulations, combination therapies and non-therapeutic agents such as radiographic dye were not included.” Clarify what you mean by “studies of generic drugs.”

Response: There is a typo error and we thank Reviewer#1 for raising it. We modified the manuscript accordingly so that the revised version now states: “Studies of generic Generic drugs, reformulations, combination therapies and non-therapeutic agents such as radiographic dye were not included”.

Comment 12: [Page 8, Lines 11-12] “Anatomical Therapeutic Chemical code”. The ATC is not a code but a classification system.

Response: We thank Reviewer#1 for raising that point. Manuscript has been modified accordingly in all concerned places (highlighted in the manuscript).

Comment 13: Figures
It is difficult to interpret the information contained in the figures due to the large range of values represented (e.g. enrolment from 1 to 900K patients). The authors could present the information in tables.

Response: So as to comply with the comment above from Reviewer #1, we added data that were extracted from some figures (those that were the most likely to be impacted by extreme values) in tables that are now embedded in a new supplementary file (S7, highlighted in the revised version of the manuscript).

Reviewer: 2
Reviewer Name: Rita Banzi
Institution and Country: IRCCS-Mario Negri Institute for Pharmacological Research, Italy
Competing Interests: I know some of the authors but currently I don't have active collaborations with them

Comment 1: General comment:
I would like to thank the BMJ Open for giving me the opportunity to review this paper. My congratulations to the authors as this analysis seems to derive from a huge work. The collection of evidence on the physio-pathology of post-marketing research is of utmost importance. Nowadays, as early approvals are increasingly tempting several regulators, it is fundamental. We should gather evidence on the ability of post-marketing research to fill the knowledge gaps at the time of approval, expand the use to different population, or optimize schedules and algorithm of treatment. It would be very important also the assessment of post-marketing research values (less artificial conditions? more pragmatic?) and its real and alleged limitations.
The paper by Zeitoun and colleagues provides a “comprehensive description of post-marketing trials registered in ClinicalTrials.gov, for a sample of drugs approved by both the FDA and EMA from 2005 to 2010.” The authors provide a very broad picture (median values and aggregate figures) that gives an overall idea on the trends and status of post marketing research. The applied methodology seems to be adequate and robust and the limitations linked to the use of one single (imperfect) register duly mentioned. Some interesting findings are presented, such as that almost 40% of the trials test drugs in indications other than those approved and the time pattern of trial inception after the first approval. Other aggregate findings are less meaningful: for example, the variability in number of trials or participants is probably a consequence of the large heterogeneity of the sample (from sorafenib to drugs for very rare diseases).

Unfortunately, this data does not allow any conclusion on the usefulness of this post-market research to patients and health care systems. In other words, if it is done to address real medical needs, commercial reasons, academic pressures or other goals. Of course, this is far beyond the aim of the submitted paper and would be possible only considering specific therapeutic areas.
My opinion is that the analysis could be of interest to the general readers of BMJ Open. However, some minor revisions could help to clarify some aspects of the manuscript.

Response: We thank Reviewer#2 very much for the numerous encouraging comments regarding our work.

Comment 2: Specific comments
Introduction
The authors list some reasons for conducting post-marketing trials (page 6, line 29-47). I would suggest to include also the studies designed to target product sampling towards selected prescribers or users, the so-called seeding trials. I think these studies represent a big issue in post-marketing research. Maybe, seeding trials can be also touched in the discussion.

Response: We thank Reviewer#2 for raising that relevant point. We changed the manuscript accordingly, both in the Intro and in the Discussion, so that the revised text now states: “Some research also suggested that a substantial proportion of post-marketing trials, even those with results eventually published in high-impact-factor journals, were designed for marketing purposes rather than medical interest [Alexander GC; Arch Internal Med 2011; Barbour V; Trials 2016].” and “For instance, prior research has shown that many post-marketing trials were “seeding trials”, designed for marketing purposes rather than scientific relevancy [Alexander GC; Arch Internal Med 2011; Barbour V; Trials 2016].”.

Comment 3: The objectives section should better match the different aspects covered in the results section. It is clear that the first aim is the description of the post-marketing studies on the drugs included in the sample. It is now stated that the paper aims to explore differences between the initial label and the specific clinical condition studied in the post-marketing trials. However, there are several other analyses in the paper, as the influence of study sponsor (industry/non-industry) and the analysis of the FDA supplemental indication, that should be reflected in the objectives.

Response: We agree with this comment from Reviewer#2 and therefore modified the text accordingly so that the revised version now states: “We aimed to characterize the total number of trials and patients studied, targeted indications, funding origin, geographical location of trials and status (e.g., completed or ongoing). We also sought to examine differences between the condition of the initial label and the specific clinical condition studied in the post-marketing trials, to assess the influence of the sponsor on the targeted indication, and to describe supplemental indications.”

Comment 4: The analysis of the FDA supplemental indication sounds a bit out of the scope of the paper because it focuses on granted not just “explored” supplemental indications. I guess, that was not planned from the beginning.

Response: Indeed, this was a post-hoc analysis. We thought that adding another element regarding the outcome of molecules over time would be interesting for researchers. If deemed inappropriate within the frame of the current paper, we could however delete that piece of analysis

Comment 5: Methods
Although based on (inevitable) arbitrary decisions (i.e. definition of post-marketing studies, leading drugs, etc.) the applied methods seem to be adequate and well described.

It would be useful to add some clarification on how the categories “acute, intermediate and chronic treatment” were defined (see comment in the results section below).

Response: We agree and took into account that comment in the revised version so that the text now states: “In brief, acute treatment was defined as expected use < 1 month, intermediate treatment as expected use from 1 month to 2 years, and chronic treatment as expected use > 2 years.”.

Comment 6: Results
1) Table 1 reports the characteristics of the 69 drugs included in the sample. It includes the number of drugs that have been approved on the basis of at least one active-controlled trial, placebo or no comparator as well as the number of patients in pivotal studies. Though interesting, the relevance of this info for the current analysis in unclear. Moreover this seems to be a finding of a previous analysis (ref 16); if so, it should be referenced.

Response: We agree that the data mentioned might sound disconnected to the main part of the current work. Therefore, we deleted them from Table 1 (highlighted in the manuscript).

Comment 7: Table 1 also reports the proportion of drugs to be used for acute, intermediate and chronic treatment. In the methods section, I was not able to find how these categories were defined.

Response: As we responded to comment #5, this point has been addressed in the Methods and the revised text now states: “In brief, acute treatment was defined as expected use < 1 month, intermediate treatment as expected use from 1 month to 2 years, and chronic treatment as expected use > 2 years.”.

Comment 8: While Figures are extremely clear and useful to understand the details on each of the included drugs, Table 2 is a bit unclear. Instead of having two separate column for industry and non-industry studies, I would suggest to report the data in lines, first all studies, then split in industry and non-industry (sometimes both industry/non industry data is not even needed as can be simply derived by subtraction).

Response: We tried to reconfigure Table 2 so as to follow comment#8 from Reviewer #2. However, it ended with a table with many lines and that was extremely long, likely unable to be incorporated in an article according to the usually available space. Yet, if deemed preferable and for the sake of clarity, we could maybe delete one of the three columns of Table 2.

Comment 9: The proportion of randomized/observational post marketing trials could be reported also in the abstract.

Response: We agree that this is an important information. We therefore added in the Abstract the rate of interventional trials among all post-marketing trials of our sample, so that the revised text now states: “A total of 6679 relevant post-marketing studies were identified; 5972 were interventional (89.4%).” However, due to limited space authorized by rules for authors from the BMJ Open, we had to eliminate some text from the Abstract to comply with the 300-word limit. Because data were frequently missing and due to the same lack of space reason, we suggest not adding it in the Abstract.

Comment 10: Discussion
It would be useful to add some references when similar (but limited) analyses are mentioned (for instance page 15, lines 40-43)

Response: We added several references in response to Comment#10, in particular in the suggested locations of the manuscript. For the sake of reading, they are not highlighted in the manuscript.

Comment 11: It should be acknowledged that this paper did not assess the relevance and usefulness of the clinical research done post-market.

Response: We agree that our analysis did not go far enough into the details of each trial and that we are unable to claim any analysis regarding relevance and usefulness of post-marketing research. We outline that limitation in the dedicated paragraph of the Discussion so that the revised version now states: “Finally, we could not identify whether post-marketing trials were relevant or useful because we did not analyze their design, endpoints, or comparators, among other factors.”.

Comment 12: If I understand correctly, the study period for the trial sample is “up to 10 years” rather than nearly 10 years (page 15, lines 43-46)

Response: We thank the reviewer for signalling that error. Indeed, our first trial started before 2005 (May, 2002 actually) and data exportation was in September 2014. We modified the text accordingly so that the revised version now states: “In addition, we chose a large study period, with a 6-year span for drug approvals, and nearly more than 10 years for the trial sample.”

Comment 13: Other comments
I found some discrepancies in the list of supplemental files order and numbering. At page 11 the “PRISMA” flowchart is cited as supplemental file S1 while it is named Figure 1 at page 32. However, Figure 1 is actually “Number of post-marketing trials and respective proportion of industry and non-industry”

Response: Again, we thank the reviewer for correcting our error. We modified the order of downloaded documents so that the resubmission is now accurate.

Comment 14: I would suggest using “study” rather than “trial” along the document as both interventional and observational studies are included in the sample.

Response: We replaced the word “trial” by “study” along the whole manuscript. However, for the ease of reading, this is not highlighted in the revised manuscript.

Comment 15: If pre-approval studies are pivotal trials, I would suggest clarifying it.

Response: Indeed, pre-approval studies that were taken into account were pivotal trials. This is already stated in the Methods. However, to clarify this, we further added in some other places of the manuscript that preapproval studies were pivotal trials. Those changes are highlighted in the text.

Rita Banzi, Mario Negri Institute for Pharmacological Research, 21 August 2017

VERSION 2 – REVIEW

REVIEWER	Enrique Seoane Vazquez Chapman University School of Pharmacy. US.
REVIEW RETURNED	19-Sep-2017

GENERAL COMMENTS	The revision of the manuscript does not address the concerns I expressed in the first review. There are two main problems with the methodology that, in my opinion, limit the value of the study: 1) the study used a definition of post-marketing that departs from the definition used by the FDA and the EMA, and 2) the study does not differentiate studies done by the sponsor or marketing authorization holder company or companies, including post-marketing studies required by the regulatory agencies to the sponsor company. Also, I do not recall if I mentioned that the data is relatively old and I would recommend to update the analysis using more recent data, for example, 2005-2016. Thank you for the opportunity to review the manuscript

REVIEWER	Rita Banzi IRCCS-Mario Negri Institute for Pharmacological Research Milan Italy I know some of the authors but currently I don't have active collaborations with them
REVIEW RETURNED	18-Sep-2017

GENERAL COMMENTS	The authors have adequately addressed all the concerns raised by the revision.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Enrique Seoane Vazquez
Institution and Country: Chapman University School of Pharmacy. US.
Competing Interests: None declared.

The revision of the manuscript does not address the concerns I expressed in the first review.

There are two main problems with the methodology that, in my opinion, limit the value of the study: 1) the study used a definition of post-marketing that departs from the definition used by the FDA and the EMA, and 2) the study does not differentiate studies done by the sponsor or marketing authorization holder company or companies, including post-marketing studies required by the regulatory agencies to the sponsor company.

Also, I do not recall if I mentioned that the data is relatively old and I would recommend to update the analysis using more recent data, for example, 2005-2016.

Thank you for the opportunity to review the manuscript

Response: As explained above, we performed a novel analysis after exclusion of the subsample of studies that were considered as premarket studies by Reviewer#1. Differentiation between regulatory required studies and other sponsored studies for the 6679 studies of our sample is unfeasible within the timeframe of the revision. So is the updating of our overall analysis.

Reviewer: 2
Reviewer Name: Rita Banzi
Institution and Country: IRCCS-Mario Negri Institute for Pharmacological Research, Milan, Italy
Competing Interests: I know some of the authors but currently I don't have active collaborations with them

The authors have adequately addressed all the concerns raised by the revision.

Response: We thank again Reviewer#2 for her favourable comments.