BMJ - Decision on Manuscript ID BMJ.2015.027196

Body: 11-Jul-2015

Dear Mr. Wang

Manuscript ID BMJ.2015.027196 entitled "Characteristics of Evidence Supporting Approval of Supplemental Indications for Prescription Drugs in the United States, 2005-2014"

Thank you for sending us this paper, which we were pleased to have the chance to consider and enjoyed reading. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it. This is because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript committee meeting, so that we will be in a better position to understand your study and to decide whether The BMJ is the right journal for it.

Many thanks again. We look forward to seeing your revised article within a month and, we hope, to reaching a decision.

** THE REPORT FROM THE MANUSCRIPT COMMITTEE MEETING, REVIEWERS' REPORTS, AND THE BMJ'S GENERAL REQUIREMENTS FOR RESEARCH PAPERS ARE AVAILABLE AT THE END OF THIS LETTER.**

First, however, please read these four important points about sending your revised paper back to us:

1. Deadline: Your revised manuscript should be returned within one month.

2. Online and print publication: All original research in The BMJ is published with open access. The full text online version of your article, if accepted after revision, will be the indexed citable version (full details are athttp://resources.bmj.com/bmj/about-bmj/the-bmjs-publishing-model), while the print and iPad BMJ will carry an abridged version of your article, usually a few weeks afterwards. This abridged version of the article is essentially an evidence abstract called BMJ pico, which we would like you to write using a template and then email it to papersadmin@bmj.com (there are more details below on how to write this using a template). Publication of research on bmj.com is definitive and is not simply interim "epublication ahead of print", so if you do not wish to abridge your article using BMJ pico, you will be able to opt for online only publication. Please let us know if you would prefer this option.
If/when your article is accepted we will invite you to submit a video abstract, lasting no longer than 4 minutes , and based on the information in your paper's BMJ pico evidence abstract. The content and focus of the video must relate directly to the study that has been accepted for publication by The BMJ, and should not stray beyond the data.

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Once the revised manuscript is prepared, you can upload it and submit it through your Author Center. When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) and Committee in the space provided. You can use this space to document any changes you make to the original manuscript and to explain your responses. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the

reviewer(s).

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Yours sincerely

Jose Merino
jmerino@bmj.com

As well as submitting your revised manuscript, we also require a copy of the manuscript with changes highlighted. Please upload this as a supplemental file with file designation 'Revised Manuscript Marked copy'.

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

INFORMATION ON REVISING THE CONTENT AND FORMAT OF YOUR ARTICLE

Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript. Members of the committee were: Elizabeth Loder (chair), Gary Collins (statistical consultant), Alison Tonks, Rubin Minhas, Wim Weber, Jose Merino, Tiago Villanueva

Decision: request revisions

Detailed comments from the meeting:

First and foremost, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

The editorial committee found the paper interesting. We think, however, that the authors need to address the multiple comments from reviewers and also improve the reporting of the design and the findings, as described below:
• The authors use many different terms, some technical, and it may be helpful to the readers to add a box explaining the terminology. The box could also include some information on the legal requirements for each type of drug approval (i.e. what does the FDA require at each step of the process?). While some terms are already explained in the text, the box would be helpful for readers. The terms that could be defined are:

1. Original indication
2. Supplemental approval
2.1 New indication
2.2 Modification of approved use
2.3 Expansion of patient population
3. Orphan drug

• We need additional information on the source of the data. What do the FDA medical reviews include? Is there a legal requirement to file these for any supplemental approval? Why were FDA medical reviews available for only 20% of supplemental approvals? Is the material in the original review sufficient?

• We assume that to evaluate the quality of the studies the authors used the data from the Drugs@FDA database in addition to the drug label. What type of data is available? Does it include a description of all trials used for the approval? Did you have to look at the publications for the trials included in the database? A box that lists the information in Drugs@FDA database and the drug labels may help readers understand the process better. Did you consider looking at published studies if the information was not provided in the drug label? Did you look at changes in black box warnings?

• The results narrative is somewhat monotonous and difficult to follow. The tables are helpful. Could you redraft the results section to make it clearer and more engaging?

• What are the legal implications of supplemental approvals? Is there less risk of sanctions for off-drug labeling if companies have a supplemental indication request in with the FDA? Does that incentivize companies to submit weak evidence just so they can point to the fact that they are trying to get approval?

• What will be the impact of the 21st Century Cures Act on the supplemental approval process?

IMPORTANT
When you revise and return your manuscript, please take note of all the following points about revising your article. Even if an item, such as a competing interests statement, was present and correct in the original draft of your paper, please check that it has not slipped out during revision.

a. In your response to the reviewers and committee please provide, point by point, your replies to the comments made by the reviewers and the editors, and please explain how you have dealt with them in the paper. It may not be possible to respond in detail to all these points in the paper itself, so please do so in the box provided

b. If your article is accepted it will then be edited, proofed, and - after your approval - published on bmj.com with open access. This open access Online First article will not be a pre-print. It will represent the full, citable, publication of that article. The citation will be year, volume, elocator (a unique identifier for that article): eg BMJ 2008;337:a145 — and this is what will appear immediately in Medline, PubMed, and other bibliographical indexes. We will give this citation in print and online, and you will need to use it when you cite your article.

c. Please write an abridged version of the article for the print and iPad BMJ using the appropriate BMJ pico template for your study's design. Please be reassured that it doesn't take long to complete this. When your BMJ pico is ready please email it to papersadmin@bmjgroup.com.The templates for you to download are at
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d. Please include these items in the revised manuscript to comply with BMJ style:

Title: this should include the study design eg "systematic review and meta-analysis”

Abstract
structured abstract including key summary statistics, as explained below (also see http://resources.bmj.com/bmj/authors/types-of-article/research)
for every clinical trial - and for any other registered study - the study registration number and name of register – in the last line of the structured abstract.

Introduction
this should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now

Methods:
for an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the manuscript urls to openly accessible websites where these materials can be found
Results
please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines http://www.equator-network.org/reporting-guidelines/sampl/

summary statistics to clarify your message. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:

For a clinical trial:
• Absolute event rates among experimental and control groups
• RRR (relative risk reduction)
• NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000)

For a cohort study:
• Absolute event rates over time (eg 10 years) among exposed and non-exposed groups
• RRR (relative risk reduction)

For a case control study:
• OR (odds ratio) for strength of association between exposure and outcome

For a study of a diagnostic test:
• Sensitivity and specificity
• PPV and NPV (positive and negative predictive values)
one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers eg STATA, but please say in the text which version you used
for articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system

Discussion
please write the discussion section of your paper in a structured way, to minimise the risk of careful explanation giving way to polemic.Please follow this structure:
statement of principal findings of the study
strengths and weaknesses of the study
strengths and weaknesses in relation to other studies, discussing important differences in results and what your study adds. Whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses (eg Cochrane reviews)
meaning of the study: possible explanations and implications for clinicians and policymakers and other researchers; how your study could promote better decisions
unanswered questions and future research

Footnotes and statements

What this paper adds/what is already known box (as described at http://resources.bmj.com/bmj/authors/types-of-article/research)

ID of ethics committee approval and name of the ethics committee/IRB; or a statement that approval was not required (see http://resources.bmj.com/bmj/authors/editorial-policies/guidelines) and a statement that participants gave informed consent before taking part

a statement that any identifiable patients have provided their signed consent to publication. Please submit, as a supplemental file, the signed BMJ patient consent form giving consent to publication in The BMJ of any information about identifiable individual patients. Publication of any personal information about a patient in The BMJ, for example in a case report or clinical photograph, will normally require the signed consent of the patient.

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a data sharing statement declaring what further information and data you are willing to make available, over and above the results reported in the paper. Suggested wording: "Data sharing: technical appendix, statistical code, and dataset [state whether any patient level data have been anonymised] are available at this repository or website OR from the corresponding author at ". If there are no such further data available, please use this wording: "Data sharing: no additional data available". For papers reporting the main results of trials of drugs or devices we require that the authors state, at a minimum, that the relevant anonymised patient level data are available on reasonable request from the authors
The BMJ has partnered with the Dryad Digital Repository datadryad.org to make open deposition easy and to allow direct linkage by doi from the dataset to The BMJ article and back - we encourage authors to use this option
funding statement (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements)
statement of the independence of researchers from funders (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements)
for studies funded or sponsored by industry (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements)
a statement describing the role of the study sponsor(s), if any, in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication
assurance, in the cover letter, that a clinical trial funded by a pharmaceutical or other commercial company follows the guidelines on good publication practice (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements)
inclusion in the list of contributors the name(s) any professional medical writer(s), specifying in the formal funding statement for the article who paid the writer. Writers and authors must have access to relevant data while writing articles.

Patient centred research
for studies that are relevant to patients we expect authors to report in their articles the extent of their study's patient-centredness, as highlighted by these questions:
did you involve patients/service users/carers/lay people in the design of this study? Please state

whether you did, and give details (Methods section)
was the development and/or selection of outcome measures informed by patients' priorities and experiences? Please give details (Methods section)
were patients/service users/carers/lay people involved in developing plans for participant recruitment and study conduct? If so, please specify how (Methods section)
have you planned to disseminate the results of the study to participants? If so how will this be done? (Describe in brief footnote)
are patients thanked in the contributorship statement or acknowledgements?
for articles reporting randomised controlled trials: did you assess the burden of the intervention on patients' quality of life and health? If so, what evaluation method did you use, and what did you find? (Methods and Results sections)

REFEREES COMMENTS

Reviewer: 1

Recommendation:

Comments:
My main concern with this study is that the authors did not compare the original indication(s) with the supplemental indication(s). Doesn't the type of study endpoint and comparator depend on the indication being studied? Therefore, if the supplemental indication differed significantly from the original indication wouldn't that affect the study design?

In addition, I have more specific concerns.

Page 5, lines 14-21:

If 50% of new drugs are approved with placebo controlled trials and 50% with uncontrolled trials does that mean that there are no new drugs approved with trials against an active comparator?

Page 6, line 10:

I would question the use of the word "rigor" here as it implies that more than the endpoints and comparators will be assessed.

Page 8, lines 37-44:

How was the study classified if both a placebo and active comparator were used? Would the classification differ depending on the indication being studied, i.e., is it more useful to use a placebo control for some types of indications and an active control for other types)?

Page 9, lines 8-10:

What was the reason for separating clinical outcomes and clinical scales?

Page 9, lines 30-34:

If a drug was originally approved for multiple indications was it counted more than once?

Page 15, lines 3-8:

A new paper in Drug Safety questions how useful the Sentinel Initiative is at present.

Page 15, lines 49-53:

From the regulators point of view there might not be an imperative to approve supplemental indications but from a patient's point of view there might be if the off-label use is not covered by insurance.

Page 17, line 8:

What kind of monitoring are the authors referring to?

Additional Questions:
Please enter your name: Joel Lexchin

Job Title: Professor

Institution: York University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: From 2011 to 2014 I was the chair of the Health Action International - Europe Association board.

Reviewer: 2

Recommendation:

Comments:
Mr. Wang and Dr. Kesselheim present a study analyzing publicly available US Food and Drug Administration (FDA) data comparing the quality of studies used for new and supplemental approvals for new drugs between 2005 and 2014. They demonstrate that rates of support with active comparator efficacy trials differ across supplemental approvals for new indications, modified use, and expansion of the patient population; that supplemental approval for use of orphan drugs in non-orphan clinical indications used studies of similar quality to those used in their original approval; and that the rates of active comparator study use in approval of supplemental indications were low overall. The work highlights the importance of tracking the use of drugs approved for supplemental indications to ensure robust capture of efficacy and safety data, especially when active comparator trials were not used in the supplemental approvals. The statistical approach is uncomplicated but reasonable. While the work is meaningful and important, addressing a few issues outlined below may strengthen the work and clarify its message.

Major:
1. The authors initially intended to use the FDA medical reviews to assess the quality of the supporting data for supplemental indication approval, but found that it only existed for 20% of the supplemental agents (which seems like an important finding in and of itself). They then went to the drug labels as their source data. The important question to resolve is: how do these two data sources differ? For example, do the FDA reviews also contain unpublished data that might not be included on the drug label? And who generates the drug labels? Is there any chance of selection bias in terms of what information gets captured on the drug labels (if, perhaps, not all reviewed studies get included on the drug label)? The authors make a good point in their limitations section that their results should be valid since they were comparing drug labels to drug labels (p. 16, line 39), but clarifying what is known about how these two data sources differ and whether drug labels have been validated as being as accurate as FDA medical reviews would nonetheless provide important information to the reader.

2. A great deal of information is presented on the original approvals and the subsequent supplemental approvals, by various subcategories. At times this information can be difficult to follow, in part because the denominators change frequently throughout the work and because single drugs could be approved for a multiple indications either initially or subsequently. In the text the authors provide more thorough information (eg, p. 12 line 42 describing the ten supplemental approvals for expanded populations that had no efficacy trials) but these data are not presented in tables 2 and 3, making these tables more difficult to follow. Furthermore, at times it is difficult to determine which proportions refer to which categories, such as "Compared to the original orphan approvals, these non-orphan supplemental approvals were supported by a similar proportion of active comparator trials (28% [11/40] vs. 24% [10/42])" (p. 13, lines 51-53) in which the 11/40 would appear to refer to the original orphan approvals, but other data elsewhere suggests that it should be the 10/42 that refer to these approvals.

To this end, consider re-formatting how the tables are laid out. Would including columns for "no comparator" (in Table 2 for example) or "no outcome trial" in Table 3 help? For example, reading across the first row of Table 2, one adds 41 supplemental approvals for new indications with active comparators to 77 with placebo comparators, getting only 118 out of the 136 total approvals. It would be more clear if the rows and columns summed to 100% each time. Likewise, I found it hard at first to understand the "modified" and "expanded" population rows in Table 2 under the Original approval column (because original approvals were not themselves modified or expanded). Those cells are describing that "of those original approvals that went on to have modified indications, 37 of the 83 had active comparators vs. 47 of the 93 new indications for these 83 drugs." Clearly that is cumbersome to spell out, but the current Tables 2 and 3 generate more confusion rather than clarifying the message. No clear solutions are evident to me, but consider taking the approach of following the drugs themselves (eg, make a table just for those drugs that went on to new indications, etc.) or expanding the tables so that one can track all the drugs in each table. The authors do have a footnote to this effect in both tables, but I did not find the footnotes informative. Expanding the tables may allow for removal of some of the text in the manuscript that repeats many of the same comparisons, allowing the reader to stay focused on the main take-home messages the

authors would like to report in the discussion.

Minor:
1. Is it possible that the excluded approvals related to "labeling revisions" (p. 6, line 38) also excluded approvals of drugs for new indications? Clarifying exactly what falls under a "labeling revision" beyond saying that these "focus mainly on administrative and/or logistical modifications" (p. 6 line 41) may help the reader understand whether bias was introduced into the sample of included approvals at this point.
2. Consider describing the rationale for not including those drugs and biologics that were not originally approved as novel therapeutic agents (p. 6 line 53) and the relative frequency of supplemental indication approvals for non-novel agents; this will be especially relevant if the number of supplemental indications for non-novel agents dwarfs the number for novel agents (ie, if this is the case, the findings of the study may have limited generalizability to all supplemental indication approvals).
3. Consider listing at the top of Appendix 1 how the drugs are arranged (chronologically, alphabetically, etc.).
4. Would it be useful to readers to know if there has been a trend in the annual number of approvals over time (p.10, line 20)?
5. The information in Table 1 is repeated in the text (p. 10, lines 23-42) – could consider removing the information from one of these two places.

Additional Questions:
Please enter your name: Matthew Kronman

Job Title: Assistant Professor, Division of Pediatric Infectious Diseases

Institution: University of Washington

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here:

END

Date Sent: 11-Jul-2015