PEER REVIEW HISTORY

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This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The regulatory approval of pharmaceuticals without a randomised controlled study: analysis of EMA and FDA approvals 1999 – 2014
AUTHORS	Hatswell, Anthony; Baio, Gianluca; Berlin, Jesse; Irs, Alar; Freemantle, Nick

VERSION 1 - REVIEW

REVIEWER	Karalis, Vangelis Univ Athens, Pharmacy
REVIEW RETURNED	31-Dec-2015

GENERAL COMMENTS	This manuscript deals with the regulatory approval of drugs without the conduct of a randomized clinical trial (RCT). The authors analyzed the number of submissions for regulatory approval to the FDA and the EMA from 1999 to 2014. They present a number of approvals without a RCT and discuss the similarities and differences between the EMA and FDA approval processes. The bottom line of this manuscript can be expressed by a question/comment whether the "treatments licensed without RCT data have an adequate benefit to risk ratio" [in the 'Conclusion']. However, I have concerns about some parts of the explanation of the results: 1. The authors refer to the number of drug approvals without a RCT, but they did not mention the total number of regulatory approvals (with and without RCT) as well as the rejection rate by the agencies. This might lead to a misinterpretation of the current approval processes and can lead to unjustified safety/efficacy concerns about the approved medications. 2. The number of approvals are only quoted without any statistical criteria of comparison or even descriptive statistics. I encourage the authors to include such type of results to enforce their arguments. 3. The type of drugs included in this analysis [Table 2] actually refers only to anticancer and orphan drugs. However, for plausible reasons (a. Oncology drugs: early in clinical practice, reduced costs etc. b. Orphan drugs: offers a range of incentives to encourage the development of these medicines) it is widely known that these two types of therapies follow a different regulatory approval rationale than the typical drugs.

	Therefore, the authors should either rephrase the manuscript title in order to express what actually did in this study or analyse all types of marketing applications (see also comment '4' below). 4. In the same vein (as in comment '3') concerns are raised on the 'exclusion criteria' listed in Table 1: - Biosimilars: The authors excluded correctly typical (chemical) generics from their analysis. However, this might not be true for biosimilars. It is not correct that biosimilars are licensed based on similarity to the existing reference products. For biosimilars very strict requirements are required by the regulatory authorities and the necessary evidence to prove equivalence is often similar to that of a new drug application. - Fixed dose combinations: It is quoted in the manuscript that "the evidence base for these products relies on that for the original products". However, this statement is not always correct since a fixed dose combination for a new drug approval actually requires a full dossier with pharmacokinetic, pharmacodynamic and safety/efficacy studies.

REVIEWER	Giovanni Tafuri European Medicines Agency/Italian Medicines Agency
REVIEW RETURNED	07-Jan-2016

GENERAL COMMENTS	The main issue is that this descriptive analysis provides little added value to the reader. Indeed, the research questions addressed by this paper have already been largely covered by previous publications. It is very well known that single-arm trials are not uncommon in marketing authorisation applications and that FDA tends to review products more quickly than EMA (or Health Canada). In addition, the information provided in the results is overall unclear and not well detailed. In particular: 1. The analysed sample is unclear: it is understood that first approvals and extensions of indications are included. Now, authors report that out of the 44 EMA approved indications, 8 were extensions of indications, while 36 were new products (how many?) or "had existing indications approved without RCT data". The difference between the "license extensions for treatment with RCTs in other indications" (i.e. extensions of indications based on uncontrolled trials?) and products that "had existing indications approved without RCT data" is unclear. The same should be clarified for the FDA approved indications. What is the difference between the 12 "licence extensions for treatment with RCT data in another approved indication" and the "treatments with existing indications approved solely on uncontrolled trials"? In general, rather than "extension of the licence for existing therapies", saying "extensions of indications" would make the text more readable. 3. At one point the data cut-off date of January 1999 is no longer applied. Which cut-off is then used for the comparisons between EMA and FDA? Results should be presented more clearly. 4. It would be useful to see the mean/median review time for each of the two agencies, not just the difference between the two. Again, authors are recommended to present results more clearly.

	5. Further to regulatory issues, the acceptance by HTA bodies of single arm trials data to support clinical and cost effectiveness assessment remains variable. This leads to EMA approved medicines that remain inaccessible to patients. Including an analysis of products approved on the basis of uncontrolled trials, receiving negative reimbursement decisions with no market access, would bring added value to the paper.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comments:
This manuscript deals with the regulatory approval of drugs without the conduct of a randomized clinical trial (RCT). The authors analyzed the number of submissions for regulatory approval to the FDA and the EMA from 1999 to 2014. They present a number of approvals without a RCT and discuss the similarities and differences between the EMA and FDA approval processes.
The bottom line of this manuscript can be expressed by a question/comment whether the “treatments licensed without RCT data have an adequate benefit to risk ratio” [in the ’Conclusion’].

However, I have concerns about some parts of the explanation of the results:

1. The authors refer to the number of drug approvals without a RCT, but they did not mention the total number of regulatory approvals (with and without RCT) as well as the rejection rate by the agencies. This might lead to a misinterpretation of the current approval processes and can lead to unjustified safety/efficacy concerns about the approved medications.

We appreciate the reviewer’s comment, and have included the number of approvals issued by each agency in the text. The number of approvals has been added to the first paragraph of Results for the EMA, and second paragraph of results for the FDA, on page 4 of the document. Previously these were shown only in Figure 2

This addition shows that whilst approvals without controlled data are not the norm (the concern of the reviewer), they are sizable in number.

2. The number of approvals are only quoted without any statistical criteria of comparison or even descriptive statistics. I encourage the authors to include such type of results to enforce their arguments.

This comment is similar to comment 4 of reviewer 2. We have included the medians and interquartile ranges of review times for each agency in the final paragraph of results (top of page 5), as well as the median in the penultimate paragraph of results (also top of page 5). Because the results we cite represent the complete “population” of decisions meeting our criteria, inferential statistics would not be appropriate.

3. The type of drugs included in this analysis [Table 2] actually refers only to anticancer and orphan drugs. However, for plausible reasons (a. Oncology drugs: early in clinical practice, reduced costs etc. b. Orphan drugs: offers a range of incentives to encourage the development of these medicines) it is widely known that these two types of therapies follow a different regulatory approval rationale than the typical drugs.
Therefore, the authors should either rephrase the manuscript title in order to express what actually did in this study or analyse all types of marketing applications (see also comment ‘4’ below).

The reviewer is correct that the majority of approvals granted without controlled trials are in oncology (which we have split in to haematology and solid tumour oncology categories), and orphan conditions. This is highlighted in the abstract, which in the 3rd paragraph shows oncology approvals represent 49 of the 76 approvals, with orphan drugs adding a further 15:

> "Over the period of the study, 76 unique indications were granted without RCT results (44 by the EMA, 60 by the FDA), demonstrating that a substantial number of treatments reach the market without undergoing study in an RCT. The majority were for haematological malignancies (34), with the next most common areas being oncology (15) and metabolic conditions (15)."

The review was, however, not limited to such conditions, rather this is a finding of the study and highly relevant, in light of recent discussions in the literature – for example reference 6: Light DW, Lexchin J. Why do cancer drugs get such an easy ride? BMJ 2015;350:h2068–h2068. doi:10.1136/bmj.h2068

We also identified in the review, 8 medicines for poisoning (included in Table 2), and 2 for general haematology – we have therefore rephrased paragraph 3 of results (page 4) to read:

> "Outside of these areas, 8 approvals were granted in poisoning or emergency medicine, and 2 in general haematology. All the approvals that were extensions of the licence for existing therapies were in either haematological oncology or solid tumour oncology."

This should make it obvious to the reader that the review was not limited to specific indications, but extended (in principle) to all medicines. The discussion then reviews this finding in light of the literature.

4. In the same vein (as in comment '3') concerns are raised on the 'exclusion criteria' listed in Table 1:
- Biosimilars: The authors excluded correctly typical (chemical) generics from their analysis. However, this might not be true for biosimilars. It is not correct that biosimilars are licensed based on similarity to the existing reference products. For biosimilars very strict requirements are required by the regulatory authorities and the necessary evidence to prove equivalence is often similar to that of a new drug application.
- Fixed dose combinations: It is quoted in the manuscript that "the evidence base for these products relies on that for the original products". However, this statement is not always correct since a fixed dose combination for a new drug approval actually requires a full dossier with pharmacokinetic, pharmacodynamic and safety/efficacy studies.

We appreciate the reviewer's clarifications to our wording, and have incorporated them in to our definitions. Whilst we our wording may have been imprecise, the concept of reliance on the efficacy of the product to a degree being demonstrated by the existing product remains true. Whilst these products may need to submit a greater volume of evidence than generics, fundamentally they remain different to novel pharmaceuticals.

Additional Questions:
Please enter your name: Vangelis Karalis

Job Title: Faculty member

Institution: National and Kapodistrian University of Athens

Reviewer: 2

Recommendation:

Comments:
The main issue is that this descriptive analysis provides little added value to the reader. Indeed, the research questions addressed by this paper have already been largely covered by previous publications. It is very well known that single-arm trials are not uncommon in marketing authorisation applications and that FDA tends to review products more quickly than EMA (or Health Canada). In addition, the information provided in the results is overall unclear and not well detailed.

Our literature search has identified no published comparisons on the number of treatments licensed without randomised data. Although we have come across examples cited in other papers (for example Glasziou, P., Chalmers, I., Rawlins, M. and McCulloch, P. (2007) 'When Are Randomised Trials

Unnecessary? Picking Signal from Noise', BMJ: British Medical Journal, 334(7589), pp. 349–351), our work represents the first systematic approach to identifying the number of treatments that are in this category.

The reviewer is also correct that there has been previous work comparing the approval time of the different regulatory bodies in oncology drugs and pharmaceuticals in general (which we cite in our discussion), however the aim of this paper was not to compare the approval times, rather the approval times were analysed alongside the approval rates for evidence of a difference in approach of the two agencies i.e. as a secondary objective. Our analysis also looks in more detail than previous studies; not limited to review time by the agency, but also differences in market availability due to delays in submission by the companies involved.

In particular:

1. The analysed sample is unclear: it is understood that first approvals and extensions of indications are included. Now, authors report that out of the 44 EMA approved indications, 8 were extensions of indications, while 36 were new products (how many?) or "had existing indications approved without RCT data". The difference between the "license extensions for treatment with RCTs in other indications" (i.e. extensions of indications based on uncontrolled trials?) and products that "had existing indications approved without RCT data" is unclear. The same should be clarified for the FDA approved indications. What is the difference between the 12 "licence extensions for treatment with RCT data in another approved indication" and the "treatments with existing indications approved solely on uncontrolled trials"? In general, rather than "extension of the licence for existing therapies", saying "extensions of indications" would make the text more readable.

We thank the reviewer for highlighting the wording which is not as clear as we intended. We have therefore completely revised Results paragraphs 1 and 2 (page 4) to be more clear on the number of treatments that were license extensions. We have also adopted the reviewer's wording of 'extensions of indications'.

3. At one point the data cut-off date of January 1999 is no longer applied. Which cut-off is then used for the comparisons between EMA and FDA? Results should be presented more clearly.

The reviewer is correct that we then remove the cut-off for the comparison of the EMA and FDA. We have therefore revised the entire paragraph and wording where this analysis is performed to be clearer. The resulting paragraphs (Results paragraphs 4 and 5) now read:

> "Searching without a date restriction for treatments approved by only one agency on the basis of only uncontrolled studies yielded a further 4 approvals. These 4 treatments, approved by the EMA in our date range, were approved prior to 1999 by the FDA with a similar data package and are used in the in the comparison of EMA and FDA approval rates and times. A total of 44 applications were made to both the EMA and the FDA without controlled results (including the 4 made to the FDA prior to 1999), with the EMA approving 35, and the FDA approving 43. Of the 34 applications approved in both regions, the EMA approval was granted a mean of 13.4 months later (median 6.7, interquartile range 4.5 to 17.2 months). This delay consisted of two parts: firstly companies submitted to the EMA a mean of 7.4 months later (median 1.5, interquartile range 0.1 to 8 months), with 28 of 34 indications submitted to the FDA first. Secondly the EMA took an average of 6.3 months longer to complete their review and approve products (median 0.2, interquartile range 0.1 to 0.3 months); in comparable approvals, the EMA review was quicker in only 3 of 34 applications leading to 30/34 products reaching the market faster in the US."

We hope these changes help the reader understand both the results and rationale for the approach.

4. It would be useful to see the mean/median review time for each of the two agencies, not just the difference between the two. Again, authors are recommended to present results more clearly.

This comment was also made by reviewer 1. As a result in addition to the mean results, we have also included medians and interquartile ranges (where possible). We agree with the reviewers that these changes make the paper clearer and give a better understanding of the distribution of outcomes.

5. Further to regulatory issues, the acceptance by HTA bodies of single arm trials data to support clinical and cost effectiveness assessment remains variable. This leads to EMA approved medicines that remain inaccessible to patients. Including an analysis of products approved on the basis of uncontrolled trials, receiving negative reimbursement decisions with no market access, would bring added value to the paper.

We agree with the reviewer that this is a topic of interest, however, it is beyond the scope of this paper; we have set out to review the licensing of products without controlled trial data – a different question to that of reimbursement (which also entails comparisons across healthcare systems). Future research however may well include this issue.

Additional Questions:
Please enter your name: Giovanni Tafuri

Job Title: National Expert on Secondment

Institution: European Medicines Agency/Italian Medicines Agency

VERSION 2 – REVIEW

REVIEWER	Vangelis Karalis Faculty of Pharmacy, National and Kapodistrian University of Athens, Greece
REVIEW RETURNED	07-Mar-2016

GENERAL COMMENTS	The aim of this manuscript is to investigate the number and type of regulatory drug approvals (based on uncontrolled, single arm, studies) over the last 15 years by the EMA and the FDA. My concerns are the following: A. The manuscript title is misleading, since the analysis presented in this study does not apply to the 'regulatory approval of pharmaceuticals' of the EMA/FDA, but only to a specific portion of them. In Table 1, the authors present the exclusion criteria of the applications used in this analysis. Also, in Table 2 one can notice that this study actually refers to studies of anticancer or orphan drugs. Thus, the title should clearly reflect what was actually done in this study, namely, analysis of the approvals of these two types of medicinal products. B. In essence, the authors (pg. 2-3 of the manuscript) conclude that a surprisingly (presumably high) number of approvals of this type are granted by both agencies and they pose the query whether the society is aware of this. However, it seems that this rationale is not fully justified since: 1) Following the exclusion criteria (of Table 1), the number of approvals without a RCT is 44/795 and 60/774 for the EMA and the FDA, respectively. Besides, some of the aforementioned approvals, with no RCT, were extensions of indications (8 out of 44 and 12 out of 60) and thus, the proportion of approvals without a RCT becomes even lower. 2) The approvals included in the analysis referred to anticancer and orphan drugs. However, it is widely known that these two types of pharmacotherapies follow a different regulatory approval philosophy than the typical drugs. For example, the need of rapid entrance in

	clinical use (oncology drugs) and to provide incentives for the encouragement of development (orphan drugs). Thus, it is not surprising that a portion of drugs is placed on the market without a RCT. 3). In the vein of comment 'A'. 4) Post-marketing surveillance applies to all medicines. In this vein, it would be interesting to analyze and statistically compare the number of drug withdraws from the market between approvals with and without a RCT. If a difference is found between these two different pathways, then the authors' arguments would be valid. C. The overall presentation gives the sense of a description with few examples. The authors are encouraged to provide statistical results and/or data to enforce their arguments (e.g., comparison between the EMA and the FDA approval rates). D. It is not sure why (mainly) biosimilars (and in a less extent fixed combination products) were excluded from the analysis. For example, In case of biosimilars, the application should include quality, safe, efficacy, and immunogenicity results (for each indication and route of administration). Thus, the application of biosimilar resembles that of a new drug application. Definitely, it cannot be considered as a duplication.

REVIEWER	Giovanni Tafuri National Expert on Secondment, European Medicines Agency, London, UK
REVIEW RETURNED	10-Mar-2016

GENERAL COMMENTS	Although most issues raised during the peer-review have been addressed/clarified, the main issue is that the paper cannot be considered as novel. Previous papers (examples could be Apolone et al. Ten years of marketing approvals of anticancer drugs in Europe: regulatory policy and guidance documents need to find a balance between different pressures. Br J Cancer. 2005 or Bertele et al. Haematological anticancer drugs in Europe: any added value at the time of approval? Eur J Clin Pharmacol. 2007) already quantified and discussed the approvals based on single arm trials. As previously mentioned, different approval times between agencies have also been largely covered in scientific literature. Also, the methodology used to count the number of products not approved by FDA is questionable and may be misleading (lines 20-27 page 5). It is indeed unclear how authors quantified products approved by EMA and rejected by FDA. Minor points: Line 46, page 5: rather than "EMA failed to approve the application" you may consider saying "EMA rejected the application" or alternatively "the company failed to receive a marketing authorisation". Line 53: what is the source of this information? Line 10-14, page 6: please elaborate more on the search performed without a date restriction.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Vangelis Karalis

Institution and Country: Faculty of Pharmacy, National and Kapodistrian University of Athens, Greece
Competing Interests: None declared

The aim of this manuscript is to investigate the number and type of regulatory drug approvals (based on uncontrolled, single arm, studies) over the last 15 years by the EMA and the FDA.

My concerns are the following:

A. The manuscript title is misleading, since the analysis presented in this study does not apply to the 'regulatory approval of pharmaceuticals' of the EMA/FDA, but only to a specific portion of them. In Table 1, the authors present the exclusion criteria of the applications used in this analysis. Also, in Table 2 one can notice that this study actually refers to studies of anticancer or orphan drugs. Thus, the title should clearly reflect what was actually done in this study, namely, analysis of the approvals of these two types of medicinal products.

Whilst we agree with the sentiment of the reviewer, in this instance we disagree with their proposed course of action. As noted by the reviewer, types of treatment other than oncology and orphan drugs (both exceptionally wide and diverse categories) were not excluded from the study – indeed 10 of the 74 approvals were outside of these two categories.

However as the reviewer states, the majority of conditions listed were in the categories of rare diseases (a term we prefer, as 'orphan' has specific conditions to regulators) – this is a key finding of the study, which we have highlighted in Paragraph 2 of the discussion:

> "The disease areas where uncontrolled studies are used for approval were primarily in oncology, with 49/74 indications (66%) being either haematological or solid tumour oncology"

To state in the title that the only areas searched were oncology and rare diseases would instead be misleading, as this does not accurately reflect the methodology, or the complete results.

B. In essence, the authors (pg. 2-3 of the manuscript) conclude that a surprisingly (presumably high) number of approvals of this type are granted by both agencies and they pose the query whether the society is aware of this.

The reviewer is correct in that we were surprised by the high rate; we have therefore revised this paragraph to be clearer about the reason for our surprise. The resulting paragraph (discussion paragraph 1, Page 6) now reads:

> "The number of approvals without supporting RCT evidence was in excess of what we had expected, with a mean of approximately 5 indications per year approved by either (or both) the EMA and the FDA. We had also expected the majority of approvals to be licence extensions of existing products, however this was not the case - only 19% of approvals were licence extensions of products demonstrated to be efficacious in RCTs in other diseases."

We have then addressed each of the reviewer's other points in turn below

However, it seems that this rationale is not fully justified since:

1) Following the exclusion criteria (of Table 1), the number of approvals without a RCT is 44/795 and 60/774 for the EMA and the FDA, respectively. Besides, some of the aforementioned approvals, with no RCT, were extensions of indications (8 out of 44 and 12 out of 60) and thus, the proportion of approvals without a RCT becomes even lower.

Whilst the number of approvals based solely on uncontrolled data are a relatively small proportion of total number approvals, in terms of the absolute number of approvals we believe these worthy of consideration – approximately 3 per year by the EMA and 4 per year by the FDA. It is this high number that surprised both us as author's (the reviewer's previous comment), and also colleagues whom we have discussed the findings.

2) The approvals included in the analysis referred to anticancer and orphan drugs. However, it is widely known that these two types of pharmacotherapies follow a different regulatory approval philosophy than the typical drugs. For example, the need of rapid entrance in clinical use (oncology drugs) and to provide incentives for the encouragement of development (orphan drugs). Thus, it is not surprising that a portion of drugs is placed on the market without a RCT.

The reviewer raises an important point, which we do discuss in the manuscript (citing previous work). In paragraph 2 of discussion (page 6) we state "This also corresponds with previous work regarding drug licensing, which shows a lower barrier to oncology drug approval.[9]".

Whilst the perceived unmet need in oncology has been used as an argument for the use of uncontrolled studies, we are not aware of a similar discussion in the literature regarding rare diseases. By being the first to investigate empirically the number of treatments approved on this basis, this original study may also promote discussion as to what an appropriate data package should consist of in different scenarios.

In the vein of comment 'A'.

4) Post-marketing surveillance applies to all medicines. In this vein, it would be interesting to analyze and statistically compare the number of drug withdraws from the market between approvals with and without a RCT. If a difference is found between these two different pathways, then the authors' arguments would be valid.

We agree with the reviewer that it would be interesting to see the results of such analyses this would be the subject of a further study. We do not however contend that these approvals are appropriate, or inappropriate, and have restated our conclusion to emphasize the main finding of the study to be the number of approvals, as opposed to taking a strong position on the appropriateness of these approvals.

C. The overall presentation gives the sense of a description with few examples. The authors are encouraged to provide statistical results and/or data to enforce their arguments (e.g., comparison between the EMA and the FDA approval rates).

In the text we have given examples where appropriate, and following acceptance of the primary paper, intended to release a research monograph / working paper detailing the circumstances surrounding each of the approvals – should the editor find it helpful we would be happy to provide this discussion as an online appendix to the study. To discuss each of these in turn however is not possible in the constraints of published paper due to both the word count required (our current summary of circumstances for each treatment is approximately 16,000 words) and interest to a general audience.

Whilst superficially attractive, we believe that statistical comparisons between the EMA and FDA would be inappropriate due to differences in processes (for example the different remits). Where fair comparisons are possible – comparisons of approval times for the same drugs and data packages, differences are presented. Three of the authors of the study lecture in statistics and have been keen to stress caution as to the appropriateness of reducing comparisons to a statistical test, when the picture is more complex.

D. It is not sure why (mainly) biosimilars (and in a less extent fixed combination products) were excluded from the analysis. For example, In case of biosimilars, the application should include quality, safe, efficacy, and immunogenicity results (for each indication and route of administration). Thus, the application of biosimilar resembles that of a new drug application. Definitely, it cannot be considered as a duplication.

The reviewer is correct that an application for a biosimilar treatment must contain details of the safety, quality and efficacy of a product. However such approvals are fundamentally different to new drug applications. In the case of biosimilars, the mechanism of action of the compound has already been demonstrated by the original product; for example the administration of EPO increases the number of red blood cells not just in theoretical models, but also in previous clinical trials.

Such prior knowledge is why biosimilar compounds were excluded from our study, as the evidence to support a decision on rituximab biosimilar (anti-CD20) is fundamentally different to that faced by regulators at present of whether to approve daratumumab (anti-CD38) for multiple myeloma, when no controlled trials are available for the product (or similar molecules).

Reviewer: 2

Reviewer Name: Giovanni Tafuri

Institution and Country: National Expert on Secondment, European Medicines Agency, London, UK
Competing Interests: None declared

Although most issues raised during the peer-review have been addressed/clarified, the main issue is that the paper cannot be considered as novel.

Previous papers (examples could be Apolone et al. Ten years of marketing approvals of anticancer drugs in Europe: regulatory policy and guidance documents need to find a balance between different pressures. Br J Cancer. 2005 or Bertele et al. Haematological anticancer drugs in Europe: any added value at the time of approval? Eur J Clin Pharmacol. 2007) already quantified and discussed the approvals based on single arm trials. As previously mentioned, different approval times between agencies have also been largely covered in scientific literature.

We thank the reviewer for their thorough review; however we disagree strongly with the assentation that the study is not novel or original.

Our literature search has identified no published comparisons on the number of treatments granted marketing authorisation without randomised data. Whilst many publications have discussed different aspects of uncontrolled studies (for example the extensive literature on the role of equipoise) or mentioned them in passing, our work represents the first systematic approach to identifying the number of treatments that are approved solely on this basis.

The papers cited by the reviewer also support the publication of our work:

- Apolone et al is restricted in scope to oncology products and examines only the pivotal study (and not entire data package) for treatments. In addition the dates included were to 2004, when the orphan drug legislation (highlighted by reviewer 1) was implemented by the EMA in 2000.
- Bertele et al. is further restricted to haematological oncology products, which results in a sample of n=11 treatments, focussing on study design and endpoints, in so doing finding that 9/17 indications were approved on the basis of 'single arm' data

Whilst both of the above are well written and researched papers, their scope and objective were clearly different to the work we have set out to do, in reviewing the data packages for over 1500 drug approvals. In not restricting the scope of our analysis, we are able to conclude not only on the number of uncontrolled approvals, but also the disease areas in which they occur. As the reviewer expected (and past papers may hint at), oncology represents the majority of cases. We do however identify rare conditions as a major source, as well as the multiple approvals that have occurred for the treatment of various poisonings.

Due to both the comprehensive nature of the study, and the number of findings of interest to different parties, we therefore fundamentally disagree with the reviewer that the study is not novel.

Also, the methodology used to count the number of products not approved by FDA is questionable and may be misleading (lines 20-27 page 5). It is indeed unclear how authors quantified products approved by EMA and rejected by FDA.

We are grateful to the referee for highlighting that the text was unclear and potentially misleading and have revised it accordingly. The resulting paragraph now fully describes how we have identified such products (page 5, paragraph 4, shown below), a process which was neither questionable nor misleading although which we acknowledge we had poorly described:

> "As the aim of our study was to look at newly approved indications for pharmaceuticals, which led to the exclusion of several types of product, listed in Table 1. Applications were compared against the exclusion criteria, and if excluded, the reason for exclusion was noted in a hierarchical fashion. If a regulatory application for a product was made to one agency but did not appear in the results for the other agency, a search with no date restriction on was performed to identify any applications made outside the review window (to ensure all comparable approvals have been included)."

The use of this methodology (the unrestricted search) in the study allowed for a further four products to be included. For example, paclitaxel for Kaposi's sarcoma, approved by the EMA in 1999, but also approved by the FDA in 1997, which would not have been identified as a comparable approval without the use of the unrestricted search.

Minor points:

Line 46, page 5: rather than "EMA failed to approve the application" you may consider saying "EMA rejected the application" or alternatively "the company failed to receive a marketing authorisation".

We are unable to locate the proposed textual change – the word 'failed' does not appear in manuscript, and

Line 53: what is the source of this information?

We believe the reviewer is referring to the paragraph below:

Even where placebo controlled RCTs are clearly unviable - serious conditions without licensed treatments and a well-established outcome (poisoning is the obvious example); new treatments are often trialled against standard care, or as an addition to existing therapy. Such controlled study designs have been used extensively in the evaluation of novel treatments for schizophrenia, and although not without challenges, could be used to assess how a new treatment performed.

We have therefore added a reference (Geddes et al.) to a paper in the BMJ which discusses the design of studies in schizophrenia.

Line 10-14, page 6: please elaborate more on the search performed without a date restriction.

As this was highlighted by the reviewer as being unclear, this section has been completely revised, as detailed above.

VERSION 3 - REVIEW

REVIEWER	Vangelis Karalis National and Kapodistrian University of Athens, Greece
REVIEW RETURNED	14-May-2016

GENERAL COMMENTS	I believe that the manuscript will be suitable for publication if the authors take into consideration the minor corrections proposed below. My comments on the answers provided by the authors are the following: A. Satisfactory. B. Satisfactory. 1. Since there is no disagreement, I suggest that you can include a similar statement in the text. 2. Again, why not stating this explanation in the manuscript instead of referring only to your previous work? 4. - C. Agree, an online appendix of the study would be helpful. However, I disagree with the rationale of the answer that the absence of (statistical) comparisons is better than applying appropriate statistical methods. D. I suggest to include a phrase explaining why biosimilars are excluded from this analysis. Even though the regulatory approval of biosimilars do not follow officially the NDA route, it is definitely not a ‘duplication’. Currently, it is widely accepted that knowledge of the theoretical action (e.g., increase of RBCs) does not suffice. Two biological products (of the same active molecule) are not considered identical in terms of safety/efficacy/etc as in case of chemical drugs.

VERSION 3 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Vangelis Karalis

Institution and Country: National and Kapodistrian University of Athens, Greece

Competing Interests: None declared

I believe that the manuscript will be suitable for publication if the authors take into consideration the minor corrections proposed below.

My comments on the answers provided by the authors are the following:

A. Satisfactory.

No revisions required

B. Satisfactory.

No revisions required

1. Since there is no disagreement, I suggest that you can include a similar statement in the text.

As requested by the reviewer, we have included text to this effect (summarised from our previous response to the reviewer) to the first paragraph of 'Discussion', with the text shown below:

> *"Although these approvals based solely on uncontrolled data are a relatively small proportion of the total number approvals, in absolute terms they number approximately 3 per year by the EMA and 4 per year by the FDA and are worthy of further scrutiny."*

2. Again, why not stating this explanation in the manuscript instead of referring only to your previous work?

As requested by the reviewer, we have included the text from our previous response to the second paragraph of 'Discussion', with the text shown below:

> *"Whilst the perceived unmet need in oncology has been used as an argument for the use of uncontrolled studies, we are not aware of a similar discussion in the literature regarding rare diseases."*

We would however highlight that none of the work cited in this instance involved the authors of this paper – we have cited the work we feel most relevant, not that which we have authored.

4. –

No revisions required

C. Agree, an online appendix of the study would be helpful.

Once this study has been published, within 6 months we will prepare a University College London 'Research report', describing in full the circumstances around each of the pharmaceuticals described in the study. Based on the number we have described thus far, we expect this to be in the region of 25,000 words – which we think would be substantially larger than an online appendix would allow for,

and would allow us to time to fully document each of the decisions. Research Reports are free to access, and hosted on the University College London website.

However, I disagree with the rationale of the answer that the absence of (statistical) comparisons is better than applying appropriate statistical methods.

Whilst we agree with the reviewer (4 of 5 authors have postgraduate qualifications in statistics) that appropriate methods should be used in all cases when statistics are helpful, in this instance there are two main reasons why we contend it would be inappropriate to perform statistical tests (for instance comparing the review time of the FDA and EMA).

Firstly, statistical testing is used to draw inferences regarding the population, when information about only a sample is available. In this case however we have reviewed all products approved within the review period. As such we have information on the entire population, and statistical inference is thus not required. One might argue that the "generalisation" here could be across different time periods, so that there is, in fact, a larger population. We would respectfully suggest that, given the evolving nature of regulatory science, different time periods are likely to define different populations of submissions, so that generalisation is not appropriate. Secondly the analysis provided can be seen as descriptive and hypothesis-generating, in the sense of stimulating thought regarding the issue of treatments approved without randomised controlled trials. We have deliberately been extremely careful in our wording of the paper to this end, so as not to encourage over-interpretation of the results (which a p-value may encourage).

D. I suggest to include a phrase explaining why biosimilars are excluded from this analysis.

Even though the regulatory approval of biosimilars do not follow officially the NDA route, it is definitely not a 'duplication'. Currently, it is widely accepted that knowledge of the theoretical action (e.g., increase of RBCs) does not suffice. Two biological products (of the same active molecule) are not considered identical in terms of safety/efficacy/etc as in case of chemical drugs.

We agree with the reviewer, who makes an excellent point. We have therefore revised our explanation in Table 2 for biosimilars in line with the reviewer's comments. The revised text is shown below:

> *"The interpretation of data from trials of biosimilars is likely to be informed by data available regarding the original drug (both in mechanism and effect on a condition). As such, biosimilar applications cannot be considered as comparable to applications for new drugs for which no external information is available"*