PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Declines in new drug launches: myth or reality? Retrospective observational study using 30 years of data from the United Kingdom.
AUTHORS	Martino, Orsolina; Ward, Derek; Simpson, Sue; Stevens, Andrew

VERSION 1 - REVIEW

REVIEWER	Daniel Carpenter Harvard University No conflicts of interest to report.
REVIEW RETURNED	30-Sep-2012

THE STUDY	The references miss some recent papers in the U.S, including an American Journal of Public Health by S. Keyhani and authors on U.S. drug innovation in comparative context. In addition, the idea that these kinds of "innovation" or "drug lag" comparisons depend on historical baselines is a central theme of study in D. Carpenter, Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA (Princeton, 2010). The supplemental documents question is not applicable here.
RESULTS & CONCLUSIONS	the authors need to consult a more American literature, which often comes to the same conclusions in debates about the FDA and about drug pricing there.

REVIEWER	Kenneth I Kaitin, Ph.D. Professor and Director Tufts Center for the Study of Drug Development Tufts University School of Medicine Boston, Massachusetts, USA I have no competing interests to declare.
REVIEW RETURNED	03-Oct-2012

THE STUDY	The authors should cite more recent analyses of drug approval trends. For example, there are several scholarly analyses recently published by the Tufts University Center for the Study of Drug Development that look at US trends through the end of the first decade of the 2000s. The majority of references cited by the authors are from the mid-1990s to 2005. More recent citations that they include are mostly for commentaries or opinion pieces. I question the validity of the analysis depicted in Figure 2. See "comments to authors", below, for details of my concerns.

RESULTS & CONCLUSIONS	The report deals very superficially with the issue of pharma industry productivity. Although it shows that, contrary to current claims, productivity has not fallen in recent years. the report provides no other insights, nor does it enhance the reader's understanding of current trends. There is no mention of regulatory issues or their impact. Similarly, there's no discussion of whether changes could be expected in the future. This could be easily assessed by looking at clinical trial starts, CTX or IND filings, or global R&D activity. In conclusion, because of the manuscript's very narrow focus, I would suggest that it is better suited to be published as a letter, rather than as a research article.
GENERAL COMMENTS	The authors set out to answer a very basic question here: are drug approval numbers in the UK over the past few decades increasing, decreasing, or staying the same. Their results answer that question, but nothing else. For example, why were was the number of approvals so low during 1985-87? This is important because it is those low numbers that cause the trend line to show a slight rise. Also, why were the numbers so high in the mid-1990s? Could it have been the result of the global AIDS epidemic, which led regulatory authorities to loosen approval standards for new drugs? The authors state that commentary on the causes of these types of trends is outside the scope of their report. But I believe that some insights are necessary to help the reader understand the context, and to reinforce the idea that drug approvals are the function of more than simply industry development efforts. I also take issue with the authors analysis depicted in Figure 2. The analysis examines two 13-year periods, with the dividing point being 1997, which happens to be a year of a record number of NCE approvals. The authors, not surprisingly, found that from that peak there were statistically significant downward trends going in both direction. However, from the previous figure, it is clear that the authors had data covering 1982-2011. So why didn't they look at two 15-year periods: 1983-1997 and 1997-2011? Could it be that the high number of approvals in 1983 and 1984, as well as in 2010 would have confounded the pretty trends shown in Figure 2? It appears that the authors cherry-picked their sample periods, discarding available data, to show the desired trends. Figure 2 should be re-done, or deleted.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comment: 1
The references miss some recent papers in the U.S, including an American Journal of Public Health by S. Keyhani and authors on U.S. drug innovation in comparative context.

Response:
This paper addresses a very different question to the one we have investigated, as it looks at the proportions of new drugs developed in each country in relation to prescription drug spending and GDP. Nevertheless, it does draw attention to the fact that there is no standard framework for assessing the therapeutic value of new drugs developed over such a long timeframe and for all classes, and we have incorporated its findings into the Introduction (para 3, p.5) and Discussion (para 3, p.11).

Comment: 2
In addition, the idea that these kinds of "innovation" or "drug lag" comparisons depend on historical baselines is a central theme of study in D. Carpenter, Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA (Princeton, 2010).

Response:
This reference provides a detailed review of the development of drug regulation in the USA. It describes the extent to which the power of the FDA as a regulator is inherently bound up in its organisational reputation and political influence, so that it shapes the debate on new drug licensing not just in the USA, but internationally. The central arguments and findings of this study are not directly relevant to the main purpose of our paper, however we do accept that more attention should be placed on regulation as a explanatory factor for the trends identified, and this reference has been incorporated into a more detailed exploration of this issue in our Discussion (para 2, pages 9-10 – see also response to comments 7 and 9).

Comment: 3
Again, the authors need to consult a more American literature, which often comes to the same conclusions in debates about the FDA and about drug pricing there.

Response:
Where relevant, we have incorporated the suggested references from all 3 reviewers (see comments 1, 2, 4, 10 & 11). As stated, these describe patterns of new drug introductions in the USA where data from the FDA is readily accessible. We sought to examine the same issue but in a different jurisdiction, i.e. the UK, where information from regulators over the timeframes considered are not easily accessible (see also our response to comment 7). Our paper does not attempt to describe drug pricing or pharmaceutical R&D productivity, so the literature on these aspects of pharmaceutical innovation is not directly relevant.

Reviewer: 2

Comment: 4
The authors should cite more recent analyses of drug approval trends. For example, there are several scholarly analyses recently published by the Tufts University Center for the Study of Drug Development that look at US trends through the end of the first decade of the 2000s. The majority of references cited by the authors are from the mid-1990s to 2005. More recent citations that they include are mostly for commentaries or opinion pieces.

Response:
The most recent references on the topic (Scannell et al., 2012; Light & Lexchin, 2012) both report analyses of trend data, as do Debnath et al (2010) and Munos (2009). However, as suggested, we have added another recent reference to the Introduction (para 2, p.4) that directly reports analyses from Tufts University Centre for the Study of Drug Development: Kaitin & DiMasi (2011). We have also incorporated this reference into the Discussion (para 3, p.10) as it adds to our comments on the issue of different levels of innovation.

Comment: 5
I question the validity of the analysis depicted in Figure 2. See "comments to authors", below, for details of my concerns.

Response:
We have addressed this point below (comment 9).

Comment: 6
The report deals very superficially with the issue of pharma industry productivity. Although it shows that, contrary to current claims, productivity has not fallen in recent years. the report provides no other insights, nor does it enhance the reader's understanding of current trends. There is no mention of regulatory issues or their impact. Similarly, there's no discussion of whether changes could be expected in the future. This could be easily assessed by looking at clinical trial starts, CTX or IND filings, or global R&D activity.

Response:
Our paper aims to offer a UK perspective on patterns of new drug introductions over the longer term, concluding that these mirror findings in the USA and refuting the widely expressed belief that this is falling. We do not attempt to consider economic productivity directly (outputs per R&D spend) and have sought to address this issue by incorporating differing perspectives and definitions of pharmaceutical innovation into our Discussion, clarifying the aspect of productivity that we have considered in this paper (as described in our responses to comments 4 and 10).

However, we do accept that more attention should be paid to regulatory issues and their impact, and our Discussion has been augmented and greatly strengthened to include these points (para 2, pp. 9-10 – see comments 1 and 8).

Assessing future trends is beyond the scope of this particular study, though we have amended the Discussion (para 4, p.11) to incorporate a recent forecasting analysis.

Comment: 7
In conclusion, because of the manuscript's very narrow focus, I would suggest that it is better suited to be published as a letter, rather than as a research article.

Response:
We fully acknowledge that the focus of the article is narrow. However, we feel that it makes an important contribution to the ongoing debate on whether pharmaceutical innovation is declining, especially given the differing perspectives and complexity in defining and measuring innovation.

We believe that the UK perspective is lacking in the current evidence base. Most published literature focuses on US trends, perhaps due to the accessibility of FDA data. There is no equivalent data source for regulatory information across longer time periods publicly available in the UK, and the data we have presented are not readily available in an electronic format. Though the British National Formulary is widely and publicly accessible, considerable work was involved in extracting and coding the data, and this is the longest and most up-to-date time period reported for a UK-specific analysis.

Comment: 8
The authors set out to answer a very basic question here: are drug approval numbers in the UK over the past few decades increasing, decreasing, or staying the same. Their results answer that question, but nothing else. For example, why were the number of approvals so low during 1985-87? This is important because it is those low numbers that cause the trend line to show a slight rise. Also, why were the numbers so high in the mid-1990s? Could it have been the result of the global AIDS epidemic, which led regulatory authorities to loosen approval standards for new drugs? The authors state that commentary on the causes of these types of trends is outside the scope of their report. But I believe that some insights are necessary to help the reader understand the context, and to reinforce the idea that drug approvals are the function of more than simply industry development efforts.

Response:

We agree that we have been conservative in our commentary on the observed trends, our intention was to describe these trends from a UK perspective and over as long a time period as could be achieved using available data. We did not directly collect data on the reasons for year on year variations, and so can only speculate based on existing published information. However, in response to this comment we have sought to further elaborate on the possible factors that may have contributed to the peaks and troughs in the trend line, focusing on the regulation and review of new medicines, and related policy issues (Discussion, para 2, pp.9-10 – see also response to comment 6).

Comment: 9
I also take issue with the authors analysis depicted in Figure 2. The analysis examines two 13-year periods, with the dividing point being 1997, which happens to be a year of a record number of NCE approvals. The authors, not surprisingly, found that from that peak there were statistically significant downward trends going in both direction. However, from the previous figure, it is clear that the authors had data covering 1982-2011. So why didn't they look at two 15-year periods: 1983-1997 and 1997-2011? Could it be that the high number of approvals in 1983 and 1984, as well as in 2010 would have confounded the pretty trends shown in Figure 2? It appears that the authors cherry-picked their sample periods, discarding available data, to show the desired trends. Figure 2 should be re-done, or deleted.

Response:
We appreciate the reviewer's concerns; however, the aim of Figure 2 was to demonstrate how claims of declining innovation could have arisen from the time periods included in published analyses. It was intended to be an illustrative point rather than a key research finding, based on the fact that most reports of declines in new drug launches are from the decade immediately following the 1997 peak. Therefore we have amended Figure 2 and the accompanying analysis to reflect this, showing just the 1997-2006 decade. In addition, we have also reduced its importance in the Results and Discussion sections and removed reference to this point from the Abstract to indicate that we are simply making a point about artefactual trends, and not trying to suggest a genuine trend on which to base our conclusions.

Reviewer: 3

Comment: 10
The issue "has the rate of biopharmaceutical innovation" declined is not well answered by looking at the number of newly approved chemical plus biological entities approved for use in the UK. A better measure would be the number of QALYs generated, or even the number of newly approved supplemental indications (see, for example, Berndt ER, Cockburn IM and Grepin KA, "The Impact of Incremental Innovation on Biopharmaceutical Drug Utilization in Original and Supplemental Indications", PharmacoEconomics 1006 24 Suppl 2:69-86),

Response:
We agree that the number of new drug approvals/launches is just one measure of innovation, and does not take into account the relative importance or impact of new drugs. As described in our response to comment 7, there is no publicly accessible dataset from the UK that adequately captures all approvals for supplemental indications, though we continue to maintain that the principal step in innovation is the development of novel chemical and biological entities. We have elaborated and strengthened our discussion of these issues (Discussion para 3, pp.10-11) and incorporated the suggested reference.

Comment: 11
Although there's some discussion of what constitutes a new chemical or biological entity, much

ambiguity persists. For example, what about radiological imaging agents -- the FDA counts these as new, but Tufts Center does not. Then there are isomers -- for example, esomeprazole (Nexium in the US) is an isomer of omeprazole (Prilosec in the US, Losec in most other countries) -- the FDA did not count esomeprazole as a new drug. What happened in the UK? What gives me some caution and suspicion is that the current authors report a maximum number of new drugs in the UK as being 34 in 1997; others report that in 1996 and 1997, the number of new drugs approved in the US was much larger -- over 50 (depending in part on whether one uses calendar year or fiscal year as the annual time frame). See, for example, Berndt, Gottschalk, Philipson and Strobeck, "Industry Funding of the FDA: Effects of PDUFA on Approval Times and Withdrawal Rates", Nature Reviews: Drug Discovery, 4(7):545-54, July 2005.

Response:
With regards to what constitutes a new chemical/biologic entity, we have added more information to the Appendix in order to clarify the areas of ambiguity described. Our definition of a new drug excludes all previously launched medicines, new formulations, generic medicines, new salts or esters of existing drugs, diagnostic products, natural products, nutraceuticals and medical foods.

We have also expanded our discussion of the different aspects of pharmaceutical innovation and incorporated the suggested reference (Discussion, para 2, p.10).

Comment: 12
Re methods being adequately described -- in addition to the above issue on what constitutes a new drug, in their presentation of regression results the authors fail to discuss how x (year) is measured -- is it a time counter equal to one in the first year (1971) or is it 1971?

Response:
Year is indeed treated as a continuous variable in the analysis (i.e. 1971, 1972 etc.). We have amended the Methods to state this (Analysis, p.7), although either approach generates the same regression equation beta coefficient, correlation coefficient and test of statistical significance.

Comment: 13
Re whether the statistical methods are appropriate, the regression residuals displayed in the Figures have a striking autoregressive property, yet there is no test for first or higher-order autocorrelation. Moreover, the regression results reported on from the pooled 1971-2011 regression are conditional on the assumption of a constant slope over the entire time period. This is counter to the results they report earlier where they find that 1978-97 there's an increasing or positive coefficient on the year measure, whereas from 1997 to 2011 there's a negative coefficient, each of which is significant. This suggests at a minimum that when the pooled regression is estimated, there should be a test for parameter equality in the 1971-97 and 1998-2011 time subperiods.

Response:
Additional analyses and comments on the 10 year slopes before and after 1997 were intended to be illustrative, pointing out the dangers in considering only short time intervals. We have amended this aspect of our results and discussion as described in our response to comment 10.

We have extended our results section to include the analyses described in the reviewer’s comment; these show equality of regression slopes pre and post-1997 and significant positive first-order autocorrelation in the residuals, as might be expected. These additional analyses do not alter our main findings that new drug launches have not declined over the 30 year time period, and any apparent recent reduction represents a return to historical levels of introductions.

Comment: 14

See my earlier discussion regarding omitted references.

Response:
Our response to this point is detailed above in our responses to comments 10 and 11.

Comment: 15
One other comments regarding relating number of new drug approvals to R&D spending. The cited R&D spending numbers are not adjusted for inflation. The NIH in the US has constructed and published a biomedical R&D price index, which rises at more than 4% on average annually since the 1980s. Just how different would the authors' review of the literature be if they looked at R&D spending adjusted for inflation is not addressed.

Response:
In the Introduction we cited published data on trends in the rate of new drugs per billion dollars spent on pharmaceutical R&D (Scannell et al., 2012). Scannell et al. report that they did adjust for inflation in their analysis and we have amended the Introduction (para 2, p.5) to clarify this.

However, in response to the reviewer's comments, we have also strengthened our discussion by incorporating the analysis by Munos (Discussion, para 5, pp.11-12) that adjusts costs for other factors (such as the rising cost of regulation) in addition to inflation.