PEER REVIEW HISTORY

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ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Variation in adverse drug reactions listed in product information for antidepressants and anticonvulsants between the USA and Europe: a comparison review of paired regulatory documents</th>
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<td>AUTHORS</td>
<td>Cornelius, Victoria; Liu, Kun; Peacock, Janet; Sauzet, Odile</td>
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VERSION 1 - REVIEW

| REVIEWER            | Lise Aagaard  
|                     | Faculty of Health  
|                     | Clinical Pharmacology  
|                     | University of Southern Denmark  
|                     | Odense, Denmark |
| REVIEW RETURNED     | 23-Nov-2015 |

GENERAL COMMENTS

The objective of this study was to compare consistency of adverse drug reactions data in public available drug product information documents for brand drugs between the United States and Europe. Secondly to assess the usefulness of information contained in documents for prescribers and patients.

The study is interesting but have several major limitations that should be addressed by the authors before the study can be considered for publication.

Title
The expression brand "drug harm" is used in the literature, but I think it is too general to use in this study. I recommend that you use the expression adverse drug reactions instead of, as this is the parameter which is compared in the study.

The word "brand" should also be deleted from the title.

Study design: Use of the expression "matched-paired drug document review" is a little bit confusing, and may not be correct. I suggest that you use "documentary study" instead.

Hence, I suggest that you reformulate the title into: "Comparison of information about adverse drug reactions listed in product information for antidepressants and anticonvulsants in the United States and Europe: a documentary study".

Abstract
The applied design should be corrected, se above comment.

It is unclear whether the product information included for each pharmaceutical substance where issued by the same marketing authorisation in both EU and the US? This information should be specified in the methods section as well as in the abstract.
Use of the expressions USPI and SmPC is correct but confusing, and I suggest, that one terminology, product information is used for both regulatory systems.

Conclusion: What are the clinical implications of the conclusions?

Strength and limitations: I suggest that only the major issues are stated here, and a section is added to the discussion, where all the stated issues can be discussed further.

Introduction
The major limitations of this section are, that previous important studies are not introduced, and therefore the results are not discussed and compared with these studies. Additionally the authors’ do not state, why is it important to compare product information for US and the EU, and particularly for the included therapeutic groups.

The following references should be included in the article:

I the above mentioned articles further links to relevant studies can be found.

The legal status and implications of the product information is not mentioned very clearly, as well as the challenges with providing the prescribers and patients with relevant information about rare occurring ADRs.

Methods
A section/table reporting the legal requirements for reporting of ADRs in the product information issued in both US and EU should be added.

Results
Dictionary for coding ADRs: Is this normal practice that this information should be added in the product information (PI)? I think this information is listed in the PI guidelines, and could be mentioned in the methods section instead of in the results.

Discussion:
Se previous comments to the insufficient discussion of the previous literature.

In the discussion of whether the differences in presented ADR
information could be explained by differences in coding, more aspects and references should be added. I suggest that these articles are considered/included:

- Maund E, Tendal B, Hróbjartsson A, Lundh A, Gøtzsche PC. BMJ. 2014 Jun 4;348:g3555. doi: 10.1136/bmj.g3555

Table 1: Add information about market authorization holder, and the date of the analysed product information material.

Table 2: Many data is presented in the table. Could it be made less busy without loosing relevant information?

Table 3: Please insert the name of the medicine in the left column.

Table 4: This table is very confusing, and parts of it may belong to the methods section? I suggest that this table is revised/deleted or data presented in another form.

Table A: This table is very informative. I suggest that you replace table 1 with this table.

Table B: This table is not necessary, the use of different coding dictionaries is common for licensing of the same substance is common.

Figure 1: What is the purpose of this diagram? You have presented background information that is obvious to the readers, and only important aspects of this process should be discussed in the article.

REVIEWER
D Nicholas Bateman
University of Edinburgh
UK

REVIEW RETURNED
03-Dec-2015

GENERAL COMMENTS
This is a paper that addresses the variability in SPCs (USPI in USA) for different drugs in different parts of the world.

Variability in advice on poisons management has been previously reported, even between the SPCs for the same active (see Wall AJB, Bateman DN, Waring WS. Variability in the quality of overdose advice in Summary of Product Characteristics (SPC) documents: gut decontamination recommendations for CNS drugs. British Journal of Clinical Pharmacology 2009; 67: 83-87.)

This article adds to this literature on SPC variation.

This variability is in part due to the way they are written by company staff and managed by regulators. Frequency of updates is driven by the regulatory cycle, and regulations about what is included by Regulators framework. This could be expanded on in the introduction.
Furthermore other pressures apply. Thus in the USA there is a need to avoid legal action, and this may contribute to a longer list of ADRs that is, as the authors seem to indicate excessive.

There is I agree a major problem is understanding what the SPC information means. I would also agree this can be completely counterproductive for patients who do not take medicines as they worry about the SPC content.

The content and context of this manuscript perhaps needs to be modified to better reflect these differences and consequences.

One other factor that might be brought out in the discussion is whether the differences seen are greater or less in drugs that have been long established (eg carbamazepine) as opposed to newer product such as gabapentin. Table 3 is the table that might assist in exploring this difference.

Can the authors also give examples of the difference in terms they are describing in Table 3
I worry that the terminology of reports may be different in different countries, whereas the organ system is the same, and this is the aspect that the authors do not seem to have examined, even though it is the more important for patients and physicians. Perhaps they could reflect on this and add some comments, or even better analysis.
Thus ECG abnormalities in one may be equated to arrhythmia risk in another, even though they are the same issue.

Analysis of cost effectiveness (mentioned in conclusions) cannot be measured from using the SPC I would submit. Neither benefit or harm can be derived from these lengthy missives. Please consider and adjust.

The suggestion of a better standardisation of the way data is presented internationally on the same topic is however well founded and an important message.

Some references lack page numbers and journal issues (12 and 22)

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1
Reviewer Name: Lise Aagaard
Institution and Country: Faculty of Health, Clinical Pharmacology, University of Southern Denmark, Odense, Denmark

Please leave your comments for the authors below

Reviewer: 1
The objective of this study was to compare consistency of adverse drug reactions data in public available drug product information documents for brand drugs between the United States and Europe. Secondly to assess the usefulness of information contained in documents for prescribers and patients.
The study is interesting but have several major limitations that should be addressed by the authors before the study can be considered for publication.
Title: The expression brand “drug harm” is used in the literature, but I think it is too general to use in this study. I recommend that you use the expression adverse drug reactions instead of, as this is the
parameter which is compared in the study. The word "brand" should also be deleted from the title. Study design: Use of the expression "matched-paired drug document review" is a little bit confusing, and may not be correct. I suggest that you use "documentary study" instead. Hence, I suggest that you reformulate the title into: "Comparison of information about adverse drug reactions listed in product information for antidepressants and anticonvulsants in the United States and Europe: a documentary study".

Author's response:
Thank you for your suggestion. We have taken out 'brand drug' and 'harm' from the title. We have included 'antidepressants and anticonvulsants' as per reviewer suggestion. The title now reads: 'Variation in adverse drug reactions listed in product information for antidepressants and anticonvulsants between the USA and Europe: a comparison review of paired regulatory documents'. We have also changed our references from ARs to ADRs for consistency throughout the manuscript.

Reviewer: 1
Abstract
The applied design should be corrected, see above comment.

Author's response:
We have removed the word 'matched'. We have kept the word 'paired' as this is the way we have analysed the results and we think it helps readers better understand that these documents theoretically should be identical in content.

Reviewer: 1
It is unclear whether the product information included for each pharmaceutical substance where issued by the same marketing authorisation in both EU and the US? This information should be specified in the methods section as well as in the abstract.

Author's response:
We have now added to p7 line 12/13 (methods) that guidance for completing the product documentation is from EMA and FDA and we have included the references and added on page 6 line 6. We have also added on p6 line 19 'We compared the content between USA and Europe for drugs marketed in both regions by the same market authorisation holder to assess consistency' In the abstract we have altered the wording to read: 'Design: A comparison review of product information documents for antidepressants and anticonvulsants concurrently marketed by the same pharmaceutical company in the USA and Europe'

Reviewer: 1
Use of the expressions USPI and SmPC is correct but confusing, and I suggest, that one terminology, product information is used for both regulatory systems.

Author's response:
We have now altered this throughout the document. We refer to 'product information documents'.

Reviewer: 1
Conclusion: What are the clinical implications of the conclusions?

Author's response:
We have removed the sentence in the conclusion around cost-effectiveness (also commented on by reviewer 2) and added in a sentence ‘In order for prescribers to provide considered risk-benefit advice across competing drug therapies to patients they need access to comprehensible and reliable ADR information’

Reviewer: 1
Strength and limitations: I suggest that only the major issues are stated here, and a section is added to the discussion, where all the stated issues can be discussed further.

Author’s response:
We have now removed the bullet point ‘Adverse drug reaction terms were required to be identical to be counted as matched’.

Reviewer: 1
Introduction
The major limitations of this section are, that previous important studies are not introduced, and therefore the results are not discussed and compared with these studies. Additionally the authors' do not state, why is it important to compare product information for US and the EU, and particularly for the included therapeutic groups.

Author’s response:
We thought it was important to include a general introduction to the issues surrounding the collection and reporting of ADRs as many BMJ open readers may not be familiar with this field. However we now realise that we have left out some important references regarding previous literature of production information comparisons so we thank the reviewer for highlighting these to us. We now include Eriksson 2014, Kesselheim 2013, Aagaard 2013, Garbe 2007, Warrer 2014, Wall 2009. A new paragraph has been added p6 line 13 and in the discussion ( and p14 & p15)

Our motivation for studying product information documents was not led by a specific question regarding antidepressants and anticonvulsants but by our interest in improving quality of summarising and reporting ADRs in general, specifically our motivation was to try and find an alternative reliable source to peer-reviewed published literature (which we have previously found to be inadequate Cornelius 2012 & Sauzet 2013). As a result we outline this motivation on p5 line 21 ‘Poor quality harm data found in our systematic review of trials for neuropathic pain led us to investigate other potential reliable sources of harm information.’ And we introduce the product information documents as a potential solution on p6 line 1 - p6 line 6, ending with ‘Consequently this publically available document is uniquely placed to be an invaluable source of information for patients, healthcare workers, researchers and regulators.’ We have now made the motivation for our work clearer by altering the last sentence in the introduction on p 6.

Reviewer: 1
The following references should be included in the article:
I the above mentioned articles further links to relevant studies can be found.

Author's response:
We thank the reviewer for these suggestions and have included these important references in the introduction and discussion.

Reviewer: 1
The legal status and implications of the product information is not mentioned very clearly, as well as the challenges with providing the prescribers and patients with relevant information about rare occurring ADRs.

Author's response:
We do include information indicating that the product information is legally required
• P5 line 23: ‘The regulatory application for marketing authorisation requires drug: manufacturers to list all known drug harm in a ‘product information document’’
• P7 line 12: ‘Regulatory guidelines from the FDA and EMA request that the manufacturers should report all adverse drug reactions’
and reference the guidance documents. If the reviewer has something specific in mind that we should include we would be happy to add.

We think we have in part addressed the challenges of providing prescribers and patients with relevant information in the discussion and conclusions. We have now added the sentence
P 17 Line 18: ‘What ADRs should be included and how to usefully present this multidimensional data to be informative to patients and prescribers requires further consideration’
Which now aligns better with our previously stated conclusion:
P 19 Line 10: ‘Identifying, selecting, summarising, and presenting multidimensional harm data should be underpinned by practical evidence-based guidelines.’

Reviewer: 1
Methods
A section/table reporting the legal requirements for reporting of ADRs in the product information issued in both US and EU should be added.
- Referenced the full guinace Complexity and vaugness -

Author’s response:
We have now included an additional table in the supplementary material summarising the guidelines for adverse reaction reporting for both USA and Europe. This is referenced in the methods section.

Reviewer: 1
Results
Dictionary for coding ADRs: Is this normal practice that this information should be added in the product information (PI)? I think this information is listed in the PI guidelines, and could be mentioned in the methods section instead of in the results.
Author’s response:
We felt it was an important to include the assessment of ‘dictionary used’ as it will impact on ADR terms which in turn may impact on the number of discrepancies found between documents. SmPC do say that MedDRA should be used whereas the USPI do not have such specific recommendations. We do state we will collect the dictionary used for coding in the methods section. As we know some readers may not be familiar with why a dictionary may be important or what a dictionary is used for we
reported the results (as we do with all items) using 1 or 2 sentences to motivate the importance of the outcome prior to giving the results.

Reviewer: 1
Discussion:
Se previous comments to the insufficient discussion of the previous literature.

Author's response:
We have now addressed this and included relevant studies.

Reviewer: 1
In the discussion of whether the differences in presented ADR information could be explained by differences in coding, more aspects and references should be added. I suggest that these articles are considered/included:
- Maund E, Tendal B, Hróbjartsson A, Lundh A, Gøtzsche PC. BMJ. 2014 Jun 4;348:g3555. doi: 10.1136/bmj.g3555

Author's response:
We thank the reviewer for this suggestion and we have now added further discussion and references regarding coding and dictionaries – top p15.

Reviewer: 1
Table 1: Add information about market authorization holder, and the date of the analysed product information material.

Author's response:
We have now swapped table 1 and supplementary table as this contains this information

Reviewer: 1
Table 2: Many data is presented in the table. Could it be made less busy without loosing relevant information?

Author's response:
We have now summarised the pertinent information from the original table 2 and included as a new table 2, the original table 2 is now included as an online supplementary table.

Reviewer: 1
Table 3: Please insert the name of the medicine in the left column.

Author's response:
We have now added the names to all tables.

Reviewer: 1
Table 4: This table is very confusing, and parts of it may belong to the methods section? I suggest that this table is revised/deleted or data presented in another form.

Author's response:
We feel this table is an important result as it display the rule-based methods used to flag signals of
ADRs from AE, none of which are statistically underpinned. This table also demonstrates that these vary between paired documents and that multiple differing rule-based methods are often used within a document. As this has not been sufficiently described in the paper we have altered the results section to make this clearer. The results section describing this table now reads: p12 line 14

‘In clinical trials many adverse events (AEs) will be recorded for each treatment and not all of these will be causally linked to the drug under investigation. Ideally a signal detection method which is statistically underpinned should be used to flag signals of ADRs from all AEs reported in a clinical trial. None of the documents used a statistical method to flag a signal but nine USA and three European documents reported rule-based approaches used. It is important to know what method has been used as this will dictate the number and type of ADRs that are flagged. The full list of differing rule-based approaches used are reported in Table 4. It can be seen that rule-based methods were not the same in three paired documents and that for seven USA documents multiple criteria were used within the same document.’

Reviewer: 1
Table A: This table is very informative. I suggest that you replace table 1 with this table.

Author’s response:
This has been swapped over as suggested.

Reviewer: 1
Table B: This table is not necessary, the use of different coding dictionaries is common for licensing of the same substance is common.

Author’s response:
We wanted to present this table as we would expect central safety data held by companies would use the same dictionaries for coding. We think this table demonstrates that the majority of documents did not report this information and we think it is important that they should. One of the documents did indicate they did not use a dictionary but used ‘investigators terminology’ so this left us wondering what the others who have not reported were using. We would like to leave this table in but in the online supplementary material.

Reviewer: 1
Figure 1: What is the purpose of this diagram? You have presented background information that is obvious to the readers, and only important aspects of this process should be discussed in the article.

Author’s response:
We wanted to outline the multiple issues in ADR reporting that need to be considered and addressed. This diagram has helped us to frame our future research objectives and we thought that it could be useful for other researchers in this field. If the reviewer feels strongly we will remove this figure but we have a preference to keep it in.

Reviewer: 2
Reviewer Name: Dr Nicholas Bateman
Institution and Country: University of Edinburgh, UK.
Please leave your comments for the authors below

Reviewer: 2
This is a paper that addresses the variability in SPCs (USPI in USA) for different drugs in different parts of the world. Variability in advice on poisons management has been previously reported, even between the SPCs
for the same active (see Wall AJB, Bateman DN, Waring WS. Variability in the quality of overdose advice in Summary of Product Characteristics (SPC) documents: gut decontamination recommendations for CNS drugs. British Journal of Clinical Pharmacology 2009; 67: 83-87.) This article adds to this literature on SPC variation. This variability is in part due to the way they are written by company staff and managed by regulators. Frequency of updates is driven by the regulatory cycle, and regulations about what is included by Regulators framework. This could be expanded on in the introduction.

Author’s response:
We thank the reviewer for these comments and we have now added these to the introduction p6 line 19/20: ‘While some variability would be anticipated due to differences in regulatory cycles between regions and construction of the documents by different company teams, we would expect that the ADR profile between paired documents would be similar as it should be based on centralised safety data.’

Reviewer: 2
Furthermore other pressures apply. Thus in the USA there is a need to avoid legal action, and this may contribute to a longer list of ADRs that is, as the authors seem to indicate excessive.

Author’s response:
We agree but we think this is a discussion point as it shows that the document is not being used for its intended purpose. The USPI guidelines are clear that only AEs where there is ‘reasonable possibility the drug has played a causal role’ should be included. Including a long list to minimise litigation is an abuse of the document whose primary purpose is to supply information to support healthcare workers. We have now included in the discussion: p 15 line 22 ‘In general the USA documents contained a larger number of ADRs and it was often unclear if these harm events were truly ADRs rather than AEs. It is possible that the over-inclusion of many AEs is made to minimise the risk of litigation since the manufacturers of the brand drug are held legally responsible if not reported.23 However the over-inclusion of AEs will make the absorption of pertinent harm information harder for prescribers and patients ‘

Reviewer: 2
There is I agree a major problem is understanding what the SPC information means. I would also agree this can be completely counterproductive for patients who do not take medicines as they worry about the SPC content.

The content and context of this manuscript perhaps needs to be modified to better reflect these differences and consequences.

One other factor that might be brought out in the discussion is whether the differences seen are greater or less in drugs that have been long established (eg carbamazepine) as opposed to newer product such as gabapentin. Table 3 is the table that might assist in exploring this difference.

Author’s response:
We did not explore this. Consistency was low across all drugs and we would be underpowered to discover a relationship with only 12 drugs included if there were one. However we have now included the reviewers suggestion of this issue into the discussion.

P12 line 14: ‘It is possible that the year of approval may be associated to lack of consistency, with only a few drugs included and low consistency across all drugs we did not explored this aspect but previous studies have examined this and found conflicting results. Eriksson et al.7 reported that drugs approved after 2000 showed higher consistency but Kesselheim et al.8 reported that length of time on the market
was not associated with consistency’

Reviewer: 2
Can the authors also give examples of the difference in terms they are describing in Table 3 I worry that the terminology of reports may be different in different countries, whereas the organ system is the same, and this is the aspect that the authors do not seem to have examined, even though it is the more important for patients and physicians. Perhaps they could reflect on this and add some comments, or even better analysis.
Thus ECG abnormalities in one may be equated to arrhythmia risk in another, even though they are the same issue.

Author’s response:
We did originally plan to undertake this analysis but we had not anticipated the number of disagreements which make it complicated to summarise. Due to the differences in coding there would be a subjective element in order to be able to categorise ADRs, for example there were occasions where several terms in one could map to one term in the matching document. In general there were many more ADRs in USPI and is was difficult to judge where the important differences lay in the absence of information on severity, as even fairly innocuous ADRs can impact significantly on QoL if severe. As a result of these difficulties we chose to only undertake a quantitative analysis for the ADR terms.
Below is a typical example of unmatched terms from two paired documents for the respiratory system:
USPI listed in ‘respiratory system’ but not in SmPC
• larynx edema
• sinusitis
SmPC listed in ‘respiratory system’ but not in USPI
• fibrosis
• inflammatory processes of varying histopathology
• pulmonary events

We acknowledge the important issue that the reviewer has raised in the discussion on p15 line 1 with the following paragraph:
‘The differences in the number of ADRs found between paired documents of the same drug may not all be real differences in the harm profile but could just be differences in ADR coding and presentation. It has been shown that ADR summaries are dependent on the dictionary used and even when the same dictionary is used there is interobserver variation due to coding conventions.19-21 With differing dictionaries used to code harm, data aggregated to different levels and lack of procedures reported, it was not possible for us to draw further conclusions within this study’

Reviewer: 2
Analysis of cost effectiveness (mentioned in conclusions) cannot be measured from using the SPC I would submit. Neither benefit or harm can be derived from these lengthy missives. Please consider and adjust.

Author’s response:
We have now removed reference and discussion to cost-effectiveness throughout the manuscript with regards to the SmPC and USPI. We have kept a reference to cost-effectiveness in the introduction ( p 5 line 19) as our original systematic review was meant to undertake a cost effectiveness analysis using ADR information reported in published trials but the data were inadequately reported and we were unable to complete this aspect of the study.

Reviewer: 2
The suggestion of a better standardisation of the way data is presented internationally on the same
topic is however well founded and an important message. Some references lack page numbers and journal issues (12 and 22)

Author's response: We have amended the reference to include page numbers and journal issue. Thank you.

### VERSION 2 – REVIEW

| REVIEWER           | D Nicholas Bateman  
|                   | University of Edinburgh  
|                   | UK  
| REVIEW RETURNED   | 06-Jan-2016  

**GENERAL COMMENTS**

Thank you  
I believe this version meets my previous comments
Variation in adverse drug reactions listed in product information for antidepressants and anticonvulsants, between the USA and Europe: a comparison review of paired regulatory documents

Victoria R Cornelius, Kun Liu, Janet Peacock and Odile Sauzet

*BMJ Open* 2016 6:
doi: 10.1136/bmjopen-2015-010599

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