PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Development in the number of clinical trial applications in Western Europe from 2007 to 2015: retrospective study of data from national competent authorities
AUTHORS	Dombernowsky, Tilde; Haedersdal, Merete; Lassen, Ulrik; Thomsen, Simon

VERSION 1 - REVIEW

REVIEWER	Prof. Syed A. A. Rizvi., PhD (Pharmaceutics)., PhD (Chemistry)., MSc., MBA., MS. Department of Pharmaceutical Sciences College of Pharmacy Health Professions Division Nova Southeastern University 3200 South University Drive Fort Lauderdale, FL 33328 USA
REVIEW RETURNED	14-Feb-2017

GENERAL COMMENTS	The manuscript lacks any information regarding the statistical analysis. The, Phase IV clinical trial or post launch surveillance is to observe, "drug's effect in various populations and any side effects associated with long-term use" and can go on for very long period of time. Similarly, other trial phases (I, II and III) could also last for several years, thus it is pertinent to report whether the clinical trials between 2007 to 2015, were newly originated between that time period or some continuing from the previous years? Also, it will be interesting to see the separated data of the types of products evaluated, such as small molecule pharmaceuticals, biologics, medical devices, etc.

REVIEWER	Prof. Dr. Mohamed Abou-El-Enein Charité Universitätsmedizin Berlin Campus Virchowklinikum (CVK) Augustenburger Platz 1 D-13353 Berlin
REVIEW RETURNED	14-Feb-2017

GENERAL COMMENTS	Comments to the Author: Thank you for the opportunity to review this manuscript. The topic is relevant and interesting, considering the limited available evidence. However, it needs a major revision by the authors. The authors have assessed the number of Clinical Trial Applications

	(CTAs) submitted to the concerned regulatory authorities in 10 western European countries. Please find my detailed comments below: Abstract: It is well-written; however, it can be further improved by addressing the following comments: • The research question and study objectives were clearly defined. However, the authors have not provided the rationale for selecting the study period. • The result section lacks scientific rigor and needs to provide more statistics about the outcome measures. For example, there is a need to include the results of effect size measures and the p-values for study outcome as well as the results of the Average Annual Growth Rate (AAGR). Introduction: • The introduction section is concise and fairly well written. Methods: • The authors have stated that they are inspired by the Hartmann study. However, Hartmann study has reported P values and R2 by using regression analysis for the calculation of Average Annual Growth Rates (AAGRs). While the authors of the current study have reported AAGRs without providing any details of their method of calculation. Furthermore, Hartman has reported clinical trial density as another outcome for assessing clinical trial applications activity. Authors are therefore strongly encouraged to closely follow Hartmann to make their methodology more transparent. Statistical Analysis: • As mentioned above, the authors need to provide more information about how the data was analyzed and which statistical programs and tests were used. • I do believe that the AAGR should be calculated by trend regression model supported by the P-value and R2. • Furthermore, multivariate linear trend regression model should be used for analyzing the AAGR to control the effect of the economic crisis on the clinical trial activity. For example, by using a solid indicator of economic activity like GDP annual growth rate. • Authors should first report an overall trend of AAGR for the whole study period (2007-2015) to address the primary research question followed by subgroup analysis separating three study periods (2007-2011, 2011-2014 and 2014-2015) instead of two study periods reported by authors (2007-2011, 2011-2015). Results: Results need to be presented more clearly by addressing the following comments: • Provide complete figure legends for all the figures and table. • Separate figures for both commercial and non-commercially sponsored trials should be provided as reported in table 1. This will give a better and clearer interpretation of the study findings.

	• No P values, CI or R2 have been reported anywhere in the manuscript and only subjective data has been reported. Authors should report objective statistical analysis as mentioned in the methods above. Discussion: Discussion provides good interpretation of the results; however, it can be further improved by addressing the following comments: • Additional limitations should be provided by the authors in the limitations section. • The authors need to explain the increase in the number of registered clinical trials in Europe despite the decrease in the number of CTAs as reported by the authors. • Authors have reported the increase in clinical trial registry in countries associated with lower clinical trials cost such as India, China and Japan as an indicator of global shift while neglecting the clinical trial registration in Europe (please refer to the following article doi: 10.1136/bmjopen-2015-008932). • The impact of implementation of voluntary harmonization procedure commend in 2009 on clinical trials should be discussed as it may have a role in stopping the decline in the RCAs numbers. Conclusion: • Authors need to make new recommendations based on the findings of this study and also provide directions for future research.

REVIEWER	Valentina Assi University of Edinburgh, UK
REVIEW RETURNED	05-Apr-2017

GENERAL COMMENTS	Dombernowsky and colleagues presented a retrospective study investigating the time trends of clinical trial applications in Western Europe as a whole from 2007 to 2015. The study presents the results for the 10 major EU countries of the area, and I wonder if the authors should have had a bolder goal of including all the EU countries of the area (they only excluded 2!). That would have helped maintain the promises of the manuscript titles of presenting the results for Western Europe. Overall the study presents clearly how the amount and type of clinical trials applications varied in the considered countries in the recent decade. However the study could benefit from corrections. Abstract: - Along with the average decrease over the period the authors should report also a related measure of variability, e.g. standard deviation, for a better understanding of the global picture. As a general rule it is good practice that, when reporting an average number, a variability measure should also be included. - The average change (and standard deviation) for the periods 2011-2014 and 2014-2015 should also be reported. Methods: - The authors included only Western European EU countries receiving more than 200 CTAs per year, as, they states, the data would represent Western Europe as a whole. It would be useful to expand on these selection criteria. What was the rationale behind them? What proportion of the total number of CTAs in Europe comes from these countries? Excluded countries might have experienced a different trend in their CTAs, would it be possible that

	the decrease in CTAs in the countries the authors selected, between 2007 and 2011, reflects an increase of CTAs in the excluded countries? Moreover the authors' definition of Western Europe is unclear. Looking at a map, it appears that only two countries were excluded, i.e. Ireland and Portugal, as Switzerland, Iceland and Norway are not part of EU. This observation makes you wonder if that selection criteria were actually necessary. The work would benefit from the inclusion of data from these two countries, as only then it could reflect the promises of its title. - Since the data were evaluated with regards to two periods, 2007-2011 and 2011-2015, it could be useful to add a light reference line in the figures as well, to help the readers. - From the tables and charts it appears that France data lacked the trial phase detail. This fact should be mentioned in the text. - Similarly UK data considered phase II and phase III together, as the authors specified in a footnote from Table 1. This should be mentioned in the text as well. Also the AAGR for these two phases combined would still be informative, hence I would encourage the authors to present it in Table 1 (possibly merging the two cells?) Results: - In the first line of this section, the authors mentioned the overall range of the CTAs submitted between 2007 and 2015, using only an approximation ("Between 6000 and 7000 CTAs"). The actual numbers, as reported in Figure 1, would improve the work accuracy and precision. As a general rule, when the precise numbers are available, approximations should not be used. - A measure of variability, such as the standard deviation, for the proportions of CTAs commercially and non-commercially sponsored would give a more precise estimate of the entity of the fluctuation across the years considered. - The Figures do not have a caption. The lack of captions can prevent a full understanding of the analyses displayed. Hence I find difficult to assess the figures of this manuscript without a proper explanation of what I am looking at. For instance I guess Figure 3 presents the absolute numbers of the CTAs in each country according to trial phases. Do the numbers consider all the CTAs between 2007 and 2015? - Page 8/29, line 18: Is it not clear whether the proportion reported (35% and 45%) are exact or an approximation like in the first line of this section. Exact proportions should be reported. - When reporting the average decrease, it would be helpful to have also an idea of the variability across the countries. The authors should report the standard deviation as well. This applies also to all the numbers in Table 1. - When possible the exact proportions should be reported. For instance in line 56 page 8/29 and line 1 page 9/29 after mentioning the countries, the authors should add the actual numbers to support their observation. This applies also to other lines of the section. - Table 1 would benefit from including a row, for each of the time intervals, displaying the overall AAGRs for the countries combined. Discussion: - An estimate of the number of large multinational trials conducted/registered in EU, and/or the proportion of multinational trials out of the total number of EU clinical trials would help assess their impact on the findings presented by this manuscript. Minor: - There are some typos. - Page 5/29 lines 1-2: The text suggests that the manuscript will only focus on the period 2007-2011, instead of 2007-2015. Possibly a

	typo. - Page 3/29 line 13: A typo: annually instead of annual. - Page 10/29 line 42: A typo: out instead of our.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 comment: The manuscript lacks any information regarding the statistical analysis.
Author response: The statistical analysis has been changed as recommended by reviewer 2. Please see the section “statistics” (page 4/20 line 6).

Reviewer 1 comment: The, Phase IV clinical trial or post launch surveillance is to observe, "drug's effect in various populations and any side effects associated with long-term use" and can go on for very long period of time. Similarly, other trial phases (I, II and III) could also last for several years, thus it is pertinent to report whether the clinical trials between 2007 to 2015, were newly originated between that time period or some continuing from the previous years?
Author response: Our study contains the number of clinical trial applications submitted per year. We assume that most clinical trials are initiated within months after the authorisation of the clinical trial. Therefore, we assume that most clinical trials are initiated within the same year as the CTA was authorised. Further, CTA for a clinical trial initiated in previous years are not included in the number of CTAs for one year (e.g. CTAs of clinical trials initiated in 2005 are not included in the number of CTAs in 2006).

Reviewer 1 comment: Also, it will be interesting to see the separated data of the types of products evaluated, such as small molecule pharmaceuticals, biologics, medical devices, etc.
Author response: This study only contains data on clinical trials of medicines. Therefore, clinical trials including e.g. medical devices are not included. As you point out, it could be interesting to evaluate the types of products investigated. We have included this comment in the conclusion section (page 13/20 line 21).

Reviewer 2 comment: Abstract: The research question and study objectives were clearly defined. However, the authors have not provided the rationale for selecting the study period.
Author response: This has been included in the abstract in the section “Outcome measures”.

Reviewer 2 comment: Abstract: The result section lacks scientific rigor and needs to provide more statistics about the outcome measures. For example, there is a need to include the results of effect size measures and the p-values for study outcome as well as the results of the Average Annual Growth Rate (AAGR).
Author response: The statistical analysis has been changed as recommended, please see the comments below. The result section of the abstract has been changed as recommended.

Reviewer 2 comment: Methods: The authors have stated that they are inspired by the Hartmann study. However, Hartmann study has reported P values and R2 by using regression analysis for the calculation of Average Annual Growth Rates (AAGRs). While the authors of the current study have reported AAGRs without providing any details of their method of calculation. Furthermore, Hartman has reported clinical trial density as another outcome for assessing clinical trial applications activity. Authors are therefore strongly encouraged to closely follow Hartmann to make their methodology more transparent.
Author response: We have changed the analysis of data so the AAGRs are now calculated in the same way as in the Hartmann study (AAGRs based on linear regressions). Please see the added section “statistics” (4/20 line 6). We have changed Table 1 so it now includes AAGR values for all three periods (2007-2015, 2007-2011, 2012-2015).
Hartmann has reported the number of CTAs per million inhabitants. He uses this to comment on

which countries run the most trials in relation to the number of inhabitants ("clinical trial density"). As we primarily discuss clinical trial activity on a global level, we do not find it necessary to include this term in our study.

Reviewer 2 comment: Statistical Analysis: As mentioned above, the authors need to provide more information about how the data was analyzed and which statistical programs and tests were used.
Author response: We have changed the analysis of data. Please see the added section "statistics" (page 4/20 line 6).

Reviewer 2 comment: Statistical Analysis: I do believe that the AAGR should be calculated by trend regression model supported by the P-value and R2.
Author response: We have changed the analysis of data as recommended. Please see the response above.

Reviewer 2 comment: Statistical Analysis: Furthermore, multivariate linear trend regression model should be used for analyzing the AAGR to control the effect of the economic crisis on the clinical trial activity. For example, by using a solid indicator of economic activity like GDP annual growth rate.
Author response: We have added information on this issue in the limitation section (page 10/20 line 11). We agree that the economic crisis may have had an influence on the number of CTAs. However, we only have few observations (nine) which makes even the simple linear regression uncertain. We find it hard to justify adding another parameter (GDP) in the model due to the few observations. Moreover, GDP from one year hardly represents a direct change in the number of CTAs in the same year (if the GDP was very low in e.g. 2008 we would expect the number of CTAs to decrease later e.g. in 2009/2010). Therefore, we believe a more complex model would be necessary. Further, several other parameters such as the EU directive and national political decisions may just as well have influenced the number of CTAs. That said, we ran a multivariate linear regression as requested. The effect of GDP was insignificant for both the summarised number of CTAs ($p = 0.87$ total, $p = 0.95$ commercially sponsored, $p = 0.55$ non-commercially sponsored) and the countries individually (we used the annual percentage change in GDP, ref: http://ec.europa.eu/eurostat/tgm/table.do?tab=table&plugin=1&language=en&pcode=tec00115). As argued above, we do not believe this analysis is valid in this case.

Reviewer 2 comment: Statistical Analysis: Authors should first report an overall trend of AAGR for the whole study period (2007-2015) to address the primary research question followed by subgroup analysis separating three study periods (2007-2011, 2011-2014 and 2014-2015) instead of two study periods reported by authors (2007-2011, 2011-2015).
Author response: We have included the AAGR for the whole study period (2007-2015) as requested (page 5/20 line 2 and Table 1). We have kept the subgroup analysis of two study periods (2007-2011 and 2012-2015) as we believe it is best to evaluate the period 2012-2015 as one period. However, we have changed the text in the result section to accommodate your comments and make the description of the results more distinct (page 5/20 line 1 and forward). We have renamed the period "2011 to 2015" "2012 to 2015" to make it clear that the year 2011 is included in the first period (2007 to 2011).

Reviewer 2 comment: Results: Provide complete figure legends for all the figures and table.
Author response: We are sorry that the figure captions and legends have not been available to you. This must be a mistake. We have tried to correct this and hope they now appear with the figures.

Reviewer 2 comment: Results: Separate figures for both commercial and non-commercially sponsored trials should be provided as reported in table 1. This will give a better and clearer interpretation of the study findings.
Author response: As we understand this comment, the request is for us to include in Table 1 the AAGRs of the distribution of CTAs per trial phase by type of sponsor (commercial and non-

commercial). Unfortunately, these data were not available from the national competent authorities of most countries and therefore not included.

Reviewer 2 comment: Results: No P values, CI or R2 have been reported anywhere in the manuscript and only subjective data has been reported. Authors should report objective statistical analysis as mentioned in the methods above.
Author response: We have changed the analysis of data as recommended (please see the response above). P-values and R2s have been added to the result sections which have been modified (page 5/20 line 1 and forward).

Reviewer 2 comment: Discussion: Additional limitations should be provided by the authors in the limitations section.
Author response: Additional limitations have been provided (page 10/20 line 1 and forward).

Reviewer 2 comment: Discussion: The authors need to explain the increase in the number of registered clinical trials in Europe despite the decrease in the number of CTAs as reported by the authors.
Author response: Please see our reply in the next section below.

Reviewer 2 comment: Discussion: Authors have reported the increase in clinical trial registry in countries associated with lower clinical trials cost such as India, China and Japan as an indicator of global shift while neglecting the clinical trial registration in Europe (please refer to the following article doi: 10.1136/bmjopen-2015-008932).
Author response: Thank you for pointing this out. It made us realize that we have not been specific enough in our distinction between clinical trials of medicines and clinical trials in general (i.e. interventional trials including clinical trials of medicines but also clinical trials investigating e.g. medical devices or surgical procedures). As stated in our introduction, the objective of this study is to investigate the development in the number of applications for authorisation of clinical trials of medicines submitted to national competent authorities and not all clinical trial applications. We have corrected the manuscript text several places to make the distinction clearer (e.g. page 1 line 4+5+17 and page 9/20 line 3+8+15+16).
Thank you for making us aware of the study by Viergever and Li (doi: 10.1136/bmjopen-2015-008932). We have read the article and referred to the article in the discussion section alongside the other studies of clinical trial registration which we have commented on (page 11/20 line 14). Studies investigating clinical trial registration by using the clinical trial databases ClinicalTrials.gov and ICTRP include not only clinical trials of medicines but also other clinical trials (e.g. clinical trials investigating medical devices or surgical procedures). Both the ICTRP and ClinicalTrials.gov include all interventional trials in the term “clinical trial”. For details on their definition of a clinical trial please go to http://www.who.int/ictrp/faq/en/#faq1 (ICTRP) and https://clinicaltrials.gov/ct2/about-studies/learn (ClinicalTrials.gov). Viergever and Li include all clinical trials (i.e. interventional trials as defined by ICTRP) in their study. Therefore, the increase in clinical trial registration in Europe as illustrated by Viergever and Li in figure 3 applies to all clinical trials and not only clinical trials of medicines. We find it plausible that there is a decrease in the number of CTAs for authorisation of clinical trials of medicines in Europe as our study finds despite an increase in trial registration for all clinical trials as illustrated by Viergever and Li.

Reviewer 2 comment: Discussion: The impact of implementation of voluntary harmonization procedure commend in 2009 on clinical trials should be discussed as it may have a role in stopping the decline in the RCAs numbers.
Author response: We have included this in the discussion section as recommended (page 12/20 line 19). However, as mentioned in the manuscript, to our knowledge, no studies have investigated the potential effects of the implementation of the Voluntary Harmonisation Procedure on the number of

clinical trials in Europe. We have not been able to find any articles which address this question. The Heads of Medicines Agencies (a part of the European Medicines Agency) has published some data on the Voluntary Harmonisation Procedure (ref: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2017_CTFG_Results_Voluntary_Harmonisation_Procedure_2009-2016.pdf). However, they do not conclude upon the impact of the procedure on the number of CTAs.

Reviewer 2 comment: Conclusion: Authors need to make new recommendations based on the findings of this study and also provide directions for future research.
Author response: We have included this in the conclusion section as recommended (page 13/20 line 17 and forward).

Reviewer 3 comment: Abstract: Along with the average decrease over the period the authors should report also a related measure of variability, e.g. standard deviation, for a better understanding of the global picture. As a general rule it is good practice that, when reporting an average number, a variability measure should also be included.
Author response: We have changed the statistical analysis as recommended by reviewer 2. Therefore, we have now reported AAGRs with p-values and R2. This has been added to the abstract in the section “Results”.

Reviewer 3 comment: Abstract: The average change (and standard deviation) for the periods 2011-2014 and 2014-2015 should also be reported.
Author response: We have changed the statistical analysis as recommended by reviewer 2. Therefore, we have now reported AAGRs with p-values and R2. This has been added to the abstract in the section “Results”.

Reviewer 3 comment: Methods: The authors included only Western European EU countries receiving more than 200 CTAs per year, as, they states, the data would represent Western Europe as a whole. It would be useful to expand on these selection criteria. What was the rationale behind them? What proportion of the total number of CTAs in Europe comes from these countries? Excluded countries might have experienced a different trend in their CTAs, would it be possible that the decrease in CTAs in the countries the authors selected, between 2007 and 2011, reflects an increase of CTAs in the excluded countries? Moreover the authors’ definition of Western Europe is unclear. Looking at a map, it appears that only two countries were excluded, i.e. Ireland and Portugal, as Switzerland, Iceland and Norway are not part of EU. This observation makes you wonder if that selection criteria were actually necessary. The work would benefit from the inclusion of data from these two countries, as only then it could reflect the promises of its title.
Author response: Thank you for your considerations on this issue. We have added information on this issue in the limitation section (page 10/20 line 1 and forward) and in the methods section (page 3/20 line 7). We defined Western Europe as the 24 countries included in the definition stated on https://simple.wikipedia.org/wiki/Western_Europe . The following six Western European EU member states have not been included: Ireland, Portugal, Finland, Greece, Luxembourg and Malta. These six EU member states together account for less than 400 CTAs per year (we do not know the exact number; we estimated this number by reading annual reports and statistics and by search in The European Clinical Trials database (please see references stated in the manuscript at page 10/20 line 4). Therefore, we estimate that the 10 Western European countries included in our study account for approximately 95% of the total number of CTAs in the Western European EU member states. As you point out, Norway, Iceland, and Switzerland is not a part of the EU. When including these countries (please see references stated in the manuscript at page 10/20 line 4), we estimate that the 10 countries included in our study account for approximately 90% of all CTAs in Western Europe.
We do not believe that it is plausible that the decrease in CTAs from 2007-2011 in the countries we

have included reflects an increase in the number of CTAs in the excluded countries: Firstly, the majority of CTAs in the EU are commercially sponsored CTAs (ref: European Medicines Agency, https://eudract.ema.europa.eu/statistics.html) and therefore usually multinational trials which often includes one or more of the 10 countries included in this study. Therefore, a decline in the total number of CTAs in these countries most likely also reflects a decline in the number of CTAs in the six excluded countries. Secondly, as stated above, the excluded countries only account for less than 400 CTAs annually and therefore do not have a considerable impact on the overall development in the number of CTAs in Western Europe.

Reviewer 3 comment: Methods: Since the data were evaluated with regards to two periods, 2007-2011 and 2011-2015, it could be useful to add a light reference line in the figures as well, to help the readers.
Author response: As we understand the request, we are recommended to add a vertical line in the figures at the year 2011 to separate data into two groups. As data in the figures are continuous from 2007 to 2015, we believe that a line may be confusing by making the readers think that data are not continuous. Therefore, we have decided not to add a vertical line in the figures.

Reviewer 3 comment: Methods: From the tables and charts it appears that France data lacked the trial phase detail. This fact should be mentioned in the text.
Author response: This information has been added to the text as suggested (page 3/20 line 9).

Reviewer 3 comment: Methods: Similarly UK data considered phase II and phase III together, as the authors specified in a footnote from Table 1. This should be mentioned in the text as well.
Author response: This information has been added to the text as suggested (page 3/20 line 9).

Reviewer 3 comment: Methods: Also the AAGR for these two phases combined would still be informative, hence I would encourage the authors to present it in Table 1 (possibly merging the two cells?)
Author response: This information has been added to Table 1 as recommended.

Reviewer 3 comment: Results: In the first line of this section, the authors mentioned the overall range of the CTAs submitted between 2007 and 2015, using only an approximation ("Between 6000 and 7000 CTAs"). The actual numbers, as reported in Figure 1, would improve the work accuracy and precision. As a general rule, when the precise numbers are available, approximations should not be used.
Author response: The text has been corrected as recommended (page 5/20 line 3).

Reviewer 3 comment: Results: A measure of variability, such as the standard deviation, for the proportions of CTAs commercially and non-commercially sponsored would give a more precise estimate of the entity of the fluctuation across the years considered.
Author response: A standard deviation has been added as recommended (page 5/20 line 6).

Reviewer 3 comment: Results: The Figures do not have a caption. The lack of captions can prevent a full understanding of the analyses displayed. Hence I find difficult to assess the figures of this manuscript without a proper explanation of what I am looking at. For instance I guess Figure 3 presents the absolute numbers of the CTAs in each country according to trial phases. Do the numbers consider all the CTAs between 2007 and 2015?
Author response: We are sorry that the figure captions and legends have not been available to you. This must be a mistake. We have tried to correct this and hope they now appear with the figures.

Reviewer 3 comment: Results: Page 8/29, line 18: Is it not clear whether the proportion reported (35% and 45%) are exact or an approximation like in the first line of this section. Exact proportions should

be reported.
Author response: The text has been corrected as recommended so the exact proportions are reported (page 5/20 line 10).

Reviewer 3 comment: Results: When reporting the average decrease, it would be helpful to have also an idea of the variability across the countries. The authors should report the standard deviation as well. This applies also to all the numbers in Table 1.
Author response: We have changed the statistical analysis as recommended by reviewer 2 (linear regressions). Table 1 has been changed and now includes indications of significance level for the AAGRs. We agree that standard deviations should have been a part of the original manuscript. However, we have now estimated the AAGRs based on trendlines through the observed number of CTs. Therefore, a calculation of the standard deviation over the yearly AAGRs would not reflect the true variability over the years - it would only reflect a very low and predictable variation in the trendline. We find that the p-values of the fitted trendlines serve as indicators of the true variability in the observed data which is of interest as pointed out in your comment.

Reviewer 3 comment: Results: When possible the exact proportions should be reported. For instance in line 56 page 8/29 and line 1 page 9/29 after mentioning the countries, the authors should add the actual numbers to support their observation. This applies also to other lines of the section.
Author response: The text has been corrected as recommended. The statistical analysis has been changed and most results are now reported as AAGR values as described in the responses to the comments from reviewer 2. Please see the result section (page 5/20 line 1 and forward).

Reviewer 3 comment: Results: Table 1 would benefit from including a row, for each of the time intervals, displaying the overall AAGRs for the countries combined.
Author response: This information has been added to the table as recommended.

Reviewer 3 comment: Discussion: An estimate of the number of large multinational trials conducted/registered in EU, and/or the proportion of multinational trials out of the total number of EU clinical trials would help assess their impact on the findings presented by this manuscript.
Author response: This information has been added to the discussion section (page 9/20 line 11).

Reviewer 3 comment: Minor: Page 5/29 lines 1-2: The text suggests that the manuscript will only focus on the period 2007-2011, instead of 2007-2015. Possibly a typo.
Author response: As stated in the method section “data were evaluated with regard to two periods; 2007 to 2011 and 2011 to 2015. The period 2007 to 2011 was specifically selected to compare our findings with the European Commission’s statement of a 25% decrease in the number of CTAs in the EU during this period”. Therefore, “2007-2011” is not a typo. However, we have changed the text to make this clearer (page 2/20 line 4 and forward).

Reviewer 3 comment: Minor: Page 3/29 line 13: A typo: annually instead of annual.
Author response: The typo has been corrected.

Reviewer 3 comment: Minor: Page 10/29 line 42: A typo: out instead of our.
Author response: The typo has been corrected.

VERSION 2 – REVIEW

REVIEWER	Prof. Syed A. A. Rizvi., PhD (Pharmaceutics)., PhD (Chemistry)., MSc., MBA., MS. Department of Pharmaceutical Sciences College of Pharmacy Health Professions Division Nova Southeastern University 3200 South University Drive Fort Lauderdale, FL 33328 USA
REVIEW RETURNED	05-May-2017

GENERAL COMMENTS	The authors have successfully addressed my concerns as well as of other reviewers. I recommend this manuscript for publication in the present form.

REVIEWER	Prof. Dr. Mohamed Abou-El-Enein Charite University Hospital, Berlin, Germany
REVIEW RETURNED	26-May-2017

GENERAL COMMENTS	Thanks for addressing all the comments adequately.