PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	To what degree are review outcomes aligned for New Active Substances (NASs) between the European Medicines Agency and the US Food and Drug Administration? A comparison based on publicly available information for NASs initially approved in the time period 2014 to 2016
AUTHORS	Kuhler, Thomas; Bujar, Magda; McAuslane, Neil; Liberti, Lawre

VERSION 1 – REVIEW

REVIEWER	Markus Ries University of Heidelberg
REVIEW RETURNED	30-Jan-2019

GENERAL COMMENTS	The true message of this work is diluted and gets lost in details. This paper is per se not uninteresting, but the language is technically convoluted and sounds legalese, even for physicians with substantial drug development experience and regulatory insight. Example (page 12): "For the 82 NASs that were approved by both agencies, the submission to FDA occurred a median (50 th percentile) 16 days before EMA (Figure 2). In terms of the variance, the 25 th percentile for the gap was that submission to FDA occurred one day after EMA and the 75 th percentile that submission to FDA occurred a median 75 days before EMA." I have no idea what you are trying to say. You may wish to apply standard methods of comparative statistics and present your results in a more intuitive way. A STROBE checklist would render the study more transparent. Is the COI statement complete and accurate?

REVIEWER	Enrique Seoane-Vazquez Chapman University, School of Pharmacy, Irvine, CA, US
REVIEW RETURNED	26-Feb-2019

GENERAL COMMENTS	Overall, this is an interesting study. See below my comments. Title: Consider revising the title. The submission is not simultaneous and the medicines were approved, not initially approved. Abstract: The objective seems to be “to compare” and not “to characterize.” This study does not have primary and secondary end points. That classification applies to studies with patients. Article summary: Page 3, lines 27-29. This study did not “identify specific reasons for outcome divergence.” (see Page 3, lines 40-45) It just mention cases when the company

	delayed the submission to one agency. Introduction: Page 6, lines 40-51. The objectives in the introduction should be the same than the objectives in the abstract. Methods: Data sources Simplify extensive inclusion and exclusion criteria. Consider using the definitions of compound type in table 1. Revise the inclusion criteria. This study does not include any radiopharmaceutical. The methods related to the period of analysis are confused. The manuscript says “The study included NAS applications approved by EMA (through the centralized procedure) or FDA or both between 1 January 2014 and 31 December 2016. The outcomes of applications that had not been determined by the latter date were tracked until 31 December 2017.” It is unclear if the results actually present NAS approved as of Dec 31, 2016 or Dec 31, 2017, or both. I may be better to select only one date for the analysis. Table 1. The criterion for establishing differences in indication seems different than the one actually used in the study. Results: Use different subtitles for each part. Do not call it parts. The way the results are presented is confusing and need rephrasing. For example, Page 11, Lines 51-54. “In total, 115 NASs were identified in terms of those approved by EMA or FDA or both initially in 2014-2016, with status tracked until the end of 2017 for the follow-on approval.” This sentence could be rephrased and simplified to: “There were 115 NAS approved by at least one of the agencies in the period 2010-2016.” It is unclear the meaning of the sentence “with status tracked until the end of 2017 for the follow-on approval.” Limitations: Include a detail account of limitations at the end of the discussion section. Explain the reasons why the period 2016-8 was selected for this analysis. The conclusions section is missing. Figures: Figure 1. Delete, the data is already included in the results section. Figure 2. Delete, this may be better explained as text in the results sections Figure 3. Delete, this may be better explained as a table. Figure 4. Delete, this may be better explained as text in the results sections Supplemental table 1. This table should include basic information for each drug. Type of drugs, approval and submission dates, orphan designation, review type, etc.

REVIEWER	James Robinson University of California Berkeley USA
REVIEW RETURNED	13-May-2019

GENERAL COMMENTS	Good paper. Should pose underlying question/theme more strongly in abstract, intro and discussion: if EMA and FDA are science based, why are their outcomes often different? First step, addressed here, is the measure extent of differences and do some analysis (FDA has more fully embraced accelerated review). Second step would be for the agencies to annually compare their results with one another and allow the scientific/clinical community decide what is appropriate and whether they should be standardized/unified.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Markus Ries
Institution and Country: University of Heidelberg
Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below
The true message of this work is diluted and gets lost in details. This paper is per se not uninteresting, but the language is technically convoluted and sounds legalese, even for physicians with substantial drug development experience and regulatory insight. Example (page 12): "For the 82 NASs that were approved by both agencies, the submission to FDA occurred a median (50 th percentile) 16 days before EMA (Figure 2). In terms of the variance, the 25 th percentile for the gap was that submission to FDA occurred one day after EMA and the 75 th percentile that submission to FDA occurred a median 75 days before EMA."
I have no idea what you are trying to say. You may wish to apply standard methods of comparative statistics and present your results in a more intuitive way.
THE LANGUAGE HAS BEEN REVIEWED THROUGHOUT THE MANUSCRIPT TO MAKE IT SIMPLER AND LESS TECHNICAL

A STROBE checklist would render the study more transparent. Is the COI statement complete and accurate?
THE LANGUAGE HAS BEEN ELABORATED AND IS MORE EXPLICIT

Reviewer: 2
Reviewer Name: Enrique Seoane-Vazquez
Institution and Country: Chapman University, School of Pharmacy, Irvine, CA, US
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
Overall, this is an interesting study. See below my comments.
Title:
Consider revising the title. The submission is not simultaneous and the medicines were approved, not initially approved.
THE TITLE HAS BEEN REWORDED TO ACCOMMODATE THE REVIEWER'S COMMENT
Abstract:
The objective seems to be "to compare" and not "to characterize."
WE HAVE CHANGED THE WORD "CHARACTERIZE" TO "COMPARE" IN THE OBJECTIVE BUT KEPT THE WORD "CHARACTERIZE" IN THE TITLE AS WE INDEED LOOK AT THE APPROVALS AND CATEGORIZE THEM INTO GROUPS, ANALYSE THE IMPLICATIONS, ETC., HENCE CHARACTERIZE THEM.
This study does not have primary and secondary end points. That classification applies to studies with patients.
THE LANGUAGE HAS BEEN REVIEWED AND THE REFERENCE TO PRIMARY AND SECONDARY ENDPOINTS HAS BEEN REMOVED.
Article summary:
Page 3, lines 27-29.
This study did not "identify specific reasons for outcome divergence." (see Page 3, lines 40-45) It just mention cases when the company delayed the submission to one agency.

WE DO NOT AGREE WITH THIS CONCLUSION; THE STUDY IDENTIFIED CASES WHEN THE COMPANY DELAYED SUBMISSION TO ONE AGENCY BUT THE STUDY DID ALSO INVESTIGATE, ANALYZE, AND DISCUSS THE OUTCOMES OF THE REGULATORY ASSESSMENT WHEN COMPANIES FILED SIMULTANEOUSLY WITH THE TWO AGENCIES – INDEED, THE LATTER PART IS AT THE CORE OF THE STUDY.

Introduction:

Page 6, lines 40-51. The objectives in the introduction should be the same than the objectives in the abstract.

COMMENT ADDRESSED – THE LANGUAGE IS NOW ALIGNED

Methods:

Data sources

Simplify extensive inclusion and exclusion criteria. Consider using the definitions of compound type in table 1.

IT IS IMPORTANT THAT STRINGENT AND UNAMBIGUOUS CRITERIA ARE APPLIED WHEN STUDIES LIKE THE CURRENT ONE ARE UNDERTAKEN. THE LIST MERELY REFLECTS THE EXTENSIVE NUMBER OF DRUG CLASSIFICATIONS THAT ARE PROVIDED BY THE LEGAL FRAMEWORKS. UNCLEARITIES ON IN/EXCLUSION CRITERIA WILL RENDER ANY FINDINGS AND CONCLUSIONS QUESTIONABLE AND MAYBE EVEN RENDER A STUDY INVALID. WE PROPOSE THE CRITERIA ARE LEFT UNCHANGED.

Revise the inclusion criteria. SEE COMMENT ABOVE. This study does not include any radiopharmaceutical.

IT IS CORRECT THAT THE STUDY DID NOT ESTABLISH THAT ANY RADIOPHARMACEUTICALS WERE SUBMITTED FOR REVIEW IN THE TIME PERIOD STUDIED BUT THE STUDY STILL CHECKED FOR THEM SO IT IS A BONA FIDE INCLUSION CRITERION.

The methods related to the period of analysis are confused. The manuscript says “The study included NAS applications approved by EMA (through the centralized procedure) or FDA or both between 1 January 2014 and 31 December 2016. The outcomes of applications that had not been determined by the latter date were tracked until 31 December 2017.” It is unclear if the results actually present NAS approved as of Dec 31, 2016 or Dec 31, 2017, or both. I may be better to select only one date for the analysis.

THE LANGUAGE HAS BEEN ELABORATED TO MORE CLEARLY EXPLAIN THE DATES AND THE RATIONALE BEHIND CHOOSING STARTING AND CUT-OFF DATES.

Table 1. The criterion for establishing differences in indication seems different than the one actually used in the study.

THE IN/EXCLUSION CRITERIA DEFINE WHAT IS IN AND OUT OF SCOPE. TABLE 1, ON THE OTHER HAND, DETAILS WHAT DATA WERE COLLECTED ON THE DRUGS THAT WERE INCLUDED IN THE STUDY (AS DEFINED BY THE INCLUSION CRITERIA). TABLE 1 ALSO DETAILS THE DIFFERENCE BETWEEN A BIOLOGIC AND A CHEMICALLY SYNTHESIZED COMPOUND SO PROVIDES SOME ADD’L GRANULARITY WHICH IS NOT PROVIDED IN THE INCLUSION CRITERIA.

Results:

Use different subtitles for each part. Do not call it parts.

THE WORD “PARTS” HAS BEEN REMOVED LEAVING THE SUBTITLES ONLY

The way the results are presented is confusing and need rephrasing.

THE LANGUAGE HAS BEEN REVIEWED THROUGHOUT THE MANUSCRIPT TO MAKE IT SIMPLER AND LESS TECHNICAL

For example,

Page 11, Lines 51-54. “In total, 115 NASs were identified in terms of those approved by EMA or FDA or both initially in 2014-2016, with status tracked until the end of 2017 for the follow-on approval.” This sentence could be rephrased and simplified to: “There were 115 NAS approved by at least one of the agencies in the period 2010-2016.”(REVIEWER’S LANGUAGE PROPOSAL HAS BEEN

ACCEPTED) It is unclear the meaning of the sentence “with status tracked until the end of 2017 for the follow-on approval.”
THIS HAS BEEN ADDRESSED IN THE METHODS SECTION BY THE ADDITION OF CLARIFYING LANGUAGE: “A DOSSIER COULD HAVE BEEN FILED TOWARDS THE END OF THE TIME PERIOD STUDIED BUT A REGULATORY DECISION WAS NOT MADE UNTIL AFTER THE 31 DECEMBER 2016. THE OUTCOMES OF APPLICATIONS THAT HAD NOT BEEN DETERMINED BY THE LATTER DATE WERE TRACKED FOR ANOTHER 12 MONTHS, THAT IS, UNTIL 31 DECEMBER 2017”.
Limitations:
Include a detail account of limitations at the end of the discussion section.
THE LIMITATIONS OFFERED IN THE “STRENGTHS AND LIMITATIONS OF THIS STUDY” ARE ALREADY ADDRESSED IN THE 3RD AND 6TH PARAGRAPH OF THE DISCUSSION. NOTWITHSTANDING THIS WE ELABORATED THE TOPIC AND INSERTED SOME ADD’L LANGUAGE READING “IT IS NOT CERTAIN, BUT REASONABLE TO ASSUME THAT SLIGHT DIFFERENCES IN DOSSIER SUBMISSION TIMING (WITHIN 91 DAYS) TO THE TWO AGENCIES ARE NOT OWING TO DIFFERENCES IN DOSSIER CONTENT BUR RATHER TO SPONSOR PROJECT MANAGEMENT CONCERNS. SUCH SEQUENTIAL FILING ENSURES AVAILABILITY OF THE NECESSARY SPONSOR RESOURCES TO PROMPTLY RESPOND TO REGULATORY CLARIFICATION QUESTIONS.”
Explain the reasons why the period 2016-8 was selected for this analysis.
THIS HAS BEEN ADDRESSED IN THE METHODS SECTION WITH THE FOLLOWING LANGUAGE: “A THREE-YEAR TIME STUDY PERIOD WAS SELECTED FOR ITS ABILITY TO PROVIDE A SUFFICIENTLY ROBUST DATA SET. AT THE TIME THE STUDY WAS CONDUCTED, 2014-2016 WAS THE MOST CURRENT THREE-YEAR SPAN FOR WHICH A FULL DATA SET WAS AVAILABLE.”
The conclusions section is missing.
A CONCLUSION IS OFFERED AT THE END OF THE DISCUSSION SECTION.
Figures:
Figure 1. Delete, the data is already included in the results section.
Figure 2. Delete, this may be better explained as text in the results sections
Figure 3. Delete, this may be better explained as a table.
Figure 4. Delete, this may be better explained as text in the results sections
WE SUGGEST TO KEEP THE FIGURES. TWO OF REVIEWERS THOUGHT THE LANGUAGE WAS RATHER TECHNICAL AND WE BELIEVE THE FIGURES ARE HELPFUL TO THE READER ILLUSTRATING THE MAIN POINTS OF THE PAPER
Supplemental table 1. This table should include basic information for each drug. Type of drugs, approval and submission dates, orphan designation, review type, etc.
THE INFORMATION CURRENTLY INCLUDED IN SUPPLEMENTARY TABLE 1 (THE GENERIC NAME OF ALL NEW ACTIVE SUBSTANCES IN THIS STUDY AND THE YEAR APPROVED BY THE US FDA AND EMA) WAS INTENDED TO BE COMPLEMENTARY RATHER THAN ESSENTIAL FOR READERS’ UNDERSTANDING OF THE ANALYSES DESCRIBED IN THIS REPORT. ADDITIONAL INFORMATION, SUCH AS THE TYPE OF DRUGS, APPROVAL AND SUBMISSION DATES, ORPHAN DESIGNATION AND REVIEW TYPE WILL BE FEATURED IN THE ANALYSES THAT WILL BE PART OF FUTURE MANUSCRIPTS BY THE AUTHORS, WHICH ARE CURRENTLY IN DEVELOPMENT.

Reviewer: 3
Reviewer Name: James Robinson
Institution and Country: University of California Berkeley USA
Please state any competing interests or state ‘None declared’: None

Please leave your comments for the authors below
Good paper. Should pose underlying question/theme more strongly in abstract, intro and discussion: (CIRS: what can be done here?) if EMA and FDA are science based, why are their outcomes often different (POINT TAKEN: OUR CONCLUSION, AS ARTICULATED IN THE DISCUSSION, IS THAT THE OUTCOMES ARE NOT OFTEN DIFFERENT: “OUR STUDY DEMONSTRATES THAT THERE GENERALLY IS ALIGNMENT BETWEEN NAS APPROVAL STATUS FOR EMA AND FDA AND THAT DRUG APPLICATIONS WERE MOSTLY APPROVED BY BOTH AGENCIES” HAVING SAID THAT, “ALTHOUGH THE SUBMITTED INDICATIONS WERE GENERALLY CONSISTENT FOR BOTH FDA AND EMA ACROSS THE COHORT, THERE WAS LESS CONCORDANCE BETWEEN THE AGENCIES FOR THE APPROVED INDICATIONS. THIS IS SOMETHING THAT NEEDS TO BE EXPLORED FURTHER…” - INDEED, THE AUTHORS ARE CURRENTLY WORKING ON SUCH A STUDY)? First step, addressed here, is the measure extent of differences and do some analysis (FDA has more fully embraced accelerated review). Second step would be for the agencies to annually compare their results with one another and allow the scientific/clinical community decide what is appropriate and whether they should be standardized/unified. WE FEEL THIS IS A POLITICAL DECISION – IN THE INTRODUCTION WE WRITE: “”WITH THEIR UNIQUE EXPERTISE, THE REGULATORY AGENCIES HAVE BEEN ENTRUSTED WITH THE GOAL TO PROTECT THE HEALTH AND THE WELLBEING OF THE PUBLIC THEY SERVE.“. NOTWITHSTANDING THIS WE HAVE INSERTED ADDITIONAL LANGUAGE IN THE DISCUSSION: WHILE NOT EVIDENCED BY THE CURRENT COHORT OF DRUGS INVESTIGATED, THE TWO AGENCIES ON OCCASION HAVE REACHED DIVERGENT AUTHORISATION CONCLUSIONS ON DRUG APPLICATIONS.[13-17] THESE DIVERGENCES HAVE BEEN CRITIQUED BY THIRD PARTIES SUCH AS ACADEMIA AND PATIENT ORGANISATIONS, REGULATORS HAVE RESPONDED WITH INCREASED TRANSPARENCY ON THEIR DECISION MAKING PROCESS BY, FOR INSTANCE, THE PUBLICATION OF ASSESSMENT REPORTS OR CLINICAL STUDY REPORTS.”

VERSION 2 – REVIEW

REVIEWER	Markus Ries University of Heidelberg
REVIEW RETURNED	11-Jul-2019

GENERAL COMMENTS	The topic is interesting and the paper has undergone some minor revisions in wording. There are major gaps in the description of methods, in particular statistics, STROBE criteria are not respected, and a study flowchart would facilitate converying the message. The authors are employed in a pharmaceutical company and have no conflict of interest in this topic related to drug development?

REVIEWER	Enrique Seoane Chapman University, School of Pharmacy and Economics Sciences Institute. USA.
REVIEW RETURNED	05-Jul-2019

GENERAL COMMENTS	The revised version of the manuscript includes most of the revisions I suggested. Title: Consider revising the title There are several drugs that were submitted before 2014 as you mention in the methods. Data sources Consider simplifying the extensive inclusion and exclusion criteria. The study only includes drugs classified by the FDA as new molecular entities (active moieties that have not been approved by

	the FDA previously, either as a single ingredient drug or as part of a combination product), and new BLAs. Data A radiopharmaceutical (gallium dotatate ga-68) approved by the FDA in the study period was excluded from the analysis. Explain. Supplementary Table 1 lists 116 drugs, the text mentions 155 drugs. Clarify. Consider tracking approvals until the end of 2018. Figures I still consider that most figures should be deleted.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

- Title: Consider revising the title There are several drugs that were submitted before 2014 as you mention in the methods.
    - Thank you for your comment. The title has been reworked as per the editorial request above and now reads: To what degree are review outcomes aligned for New Active Substances (NASs) between the European Medicines Agency and the US Food and Drug Administration? A comparison based on publicly available information for NASs initially approved in the time period 2014 to 2016
    - "…several drugs were submitted before 2014 as you mention in the methods." refers to a sentence in the Methods section reading "Applications were included in the study when dossiers were filed before 1 January 2014, but a regulatory decision was made within the study time period." We don't believe this level of detail necessarily has to be reflected in the title.
    - While reviewing this part of the Methods section we introduced a clarification in said sentence such that it now reads: Applications were included in the study when dossiers were filed before 1 January 2014, but a regulatory decision was not made until within the study time period.
    - Similarly, the sentence immediately following the on above has been rephrased to improve clarity and it now reads: Similarly, although the inclusion criterion was approval by one or both agencies by 31 December 2016, outcomes were tracked for another 12 months to account for a time lag, that is, until 31 December 2017.
- Data sources: Consider simplifying the extensive inclusion and exclusion criteria. The study only includes drugs classified by the FDA as new molecular entities (active moieties that have not been approved by the FDA previously, either as a single ingredient drug or as part of a combination product), and new BLAs.
    - Thank you for your comment and we do agree the list is long.

Having said that, the list merely reflects the extensive number of drug classifications that are provided by the legal frameworks in both the US and the EU. It is true that the study focuses on "innovative" drugs per the in/exclusion criteria.

For these very reasons, we believe it is important that stringent and unambiguous criteria are applied to allow for comparisons with other similar studies, past, current, or future ones. Ambiguities on in/exclusion criteria will (as opposed to may) limit the value of the conclusions.

Hence, we propose the criteria are left unchanged.

- Data: A radiopharmaceutical (gallium dotatate ga-68) approved by the FDA in the study period was excluded from the analysis. Explain.
    - Thank you for your comment. Gallium dotatate ga-68 does not meet our NAS inclusion criteria as the substance was used in Europe as a medicinal product for 10 years. This is in line with the EMA decision regarding the categorization of this product.
        i. "This is an application based on "well established medicinal use" according to Directive 2001/83/EC. Therefore, it is possible to replace results of pharmacological and toxicological tests or clinical trials by detailed references to published scientific literature (information available in the public domain). The applicant has demonstrated that edotreotide has a well-established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety, at least 10 years have passed since its first systematic and documented use as a medicinal product in the European Union and has been extensively used for the 10-year period through Europe."

        ii. https://www.ema.europa.eu/en/documents/assessment-report/somakit-toc-epar-public-assessment-report_en.pdf

        iii. NAS listing: https://www.ema.europa.eu/en/documents/leaflet/human-medicines-highlights-2016_en.pdf

- Supplementary Table 1 lists 116 drugs, the text mentions 155 drugs. Clarify.
    - Thank you for your comment. The text mentions 115 drugs (not 155). Notwithstanding this, the supplementary table was updated and corrected to remove one product (therefore tallying to 115 as per text). The change is removal of 'ombitasivr; paritaprevir; ritonavir' – this substance was removed as part of the peer-review as the EMA and FDA approved products differed – Viekira Pak (FDA) was approved as ombitasvir, paritaprevir, ritonavir tablets co-packaged with dasabuvir tablet Viekrax (EMA) as a single fixed-dose combination tablet containing ombitasvir, paritaprevir, ritonavir and dasabuvir.

- Consider tracking approvals until the end of 2018.
    - Thank you for the comment to which we agree with in principle. We believe that the currently selected three-year time period provides a sufficiently robust data set and that no significant policy changes have occurred in the last year to expect the inclusion of 2018 to alter the outcomes. Hence, we suggest a re-analysis when a second three-year cohort can be analyzed, and its results be compared with the outcomes of the current paper. In this way macro trends could potentially be identified.

- Figures: I still consider that most figures should be deleted.
    - Thank you for your comment but as we stated during the first review cycle, we believe figures are helpful to the reader illustrating the main points of the paper. Indeed, another reviewer suggested additional graphics to be included, vide infra.

Reviewer: 1

- There are major gaps in the description of methods, in particular statistics, STROBE criteria are not respected
    - Thank you for the comment. The paper does not deal with any epidemiological studies, so the STROBE checklist does not apply.
- A study flowchart would facilitate conveying the message.
    - Thank you for the comment to which we agree. A flow chart illustrating the compound selection process has been added.
- The authors are employed in a pharmaceutical company and have no conflict of interest in this topic related to drug development?
    - Please be advised the COIs are provided truthfully by each author – the paper is an analysis of facts available in the public domain and there are no advocacy issues promoted or policy suggestions forwarded. The paper is an impartial analysis and reporting of findings.
    - The author affiliation section shows that the corresponding author is employed by a pharmaceutical company, but the co-authors all work for a well-known independent research institution.