Article details: 2017-0001	
Title	Publication of confirmatory studies required by Health Canada for drugs approved under a Notice of Compliance with conditions: a cohort study
Authors	Joel Lexchin MSc MD
Reviewer 1	Dr. Bradley Mitchelmore PharmD BSc
Institution	Canadian Agency for Drugs and Technologies in Health, Ottawa, Ont.
General comments (author response in bold)	1) The search was not comprehensive; it should include at least 2+ databases and a grey literature search. EMBASE would have been beneficial as it is more European-focused and may have identified some studies that met EMA and HC needs. The screening process for inclusion was also not clear, it should be conducted by 2 reviewers and have a resolution process like a standard systematic review. Given that the response rate was not 100%, and your overall sample is small, missing a small number studies could skew the results more significantly. **The search was repeated for Embase and a second person was involved in the screening the Qualifying Notices for studies to be included. A grey literature search was not done since this literature would not typically be identifiable or readily available to health care practitioners.** 2) Context should be added; there should be additional information provided about the number of studies that were granted NOC/c, and then the outstanding time that some have been without a confirmatory study (as this is quite significant for all regulatory bodies as they aren't often agressive in following up for completion of confirmatory studies). **Information has been added about the total number of NOC/c at the time when this study was undertaken. The objective of this study was to document publication of confirmatory studies where the NOC/c was fulfilled and therefore there was no information added about the outstanding time for NOC/c that have not been fulfilled.** 3) Wording around results should be more clear, I found the results as presented difficult to follow. There are a lot of qualifiers such as "potentially" because of the lack of response from some companies. This impacts the readability and makes the results more difficult to interpret. It may be useful to provide the results with the following structure: "Using the following assumptions... (list the assumptions that the studies you found were the actual studies used) ...the percentage of..." and so on. An additional table outlining the overall results and not just for the detailed results, would also improve readability and clarity around your findings. **I thank the reviewer for this suggestion wording and have used the suggestion to begin the Interpretation section. Rather than a table, Figure 1 (the flow diagram) is used to summarize the results.** 4) Minor issues: P11, Line 22-24, avoid using terms like "almost 3/4" as this impacts readability and is not accurate and you sample is small **The exact percentage has been given.** Change "doctors" to "healthcare practitioners" throughout, as they are not the only users of this information. **The change has been made.**
Reviewer 2	Dr. Suhail Mulla PhD MSc BSc
Institution	Canadian Agency for Drugs and Technologies in Health, Toronto, Ont.
General comments (author response in bold)	General comments 1. As this is a retrospective cohort study, I would strongly advise that the author ensures the manuscript adheres to the STROBE reporting guideline. **The STROBE guidelines were reviewed and as a result "a cohort study" was added to the title.** Specific comments 1. Page 5: "… articles by Lexchin (3) and Law (5)…" What was the rationale for using these articles as sources in addition to the two Health Canada databases? **These two studies listed the NOC/c that had been granted and looked at whether they had been fulfilled. They were used in identifying drugs for which NOC/c had been granted.** 2. Page 6: "Only confirmatory studies on efficacy/effectiveness were identified." This can be interpreted in one of two ways. First, the author only sought confirmatory studies on efficacy/effectiveness. Second, Health Canada only requested confirmatory studies on efficacy/effectiveness. My suspicion is that it's the former, based on the subsequent sentence, but I would appreciate clarification. If true, this also brings up another point: were there confirmatory studies on safety that were required by Health Canada across the study sample? If so, it needs to be clear (throughout the manuscript) that the sample under study was restricted to efficacy/effectiveness evaluations. **It is now made clear that Health Canada only required confirmatory studies about efficacy/effectiveness and not safety alone.** 3. Page 6: "A web search … repeated in the first week of December 2015…" The last update is now over one year old. Would it be worth repeating the update for timeliness? **The search was repeated in the first week of February 2017 and this information has been added to the Methods.** 4. Page 9: "A search of clinicaltrials.gov, Google and PubMed yielded no information for 8 (13%) of the 61 confirmatory studies." "The companies that responded identified a total of 28 unique publications that reported on 30 studies." "When companies did not respond, there were 19 publications (for 20 studies, one publication reported on 2 studies for raltegravir) that were independently identified and no corresponding publication was found for 8 studies." "Therefore, potentially 50 of the 61 confirmatory studies (82%) were eventually published in 47 publications." Based on the chain of mathematics that the author lays out in this section, i.e. 60-(30+20+8), there are three unaccounted studies. Could the author please explain the apparent discrepancy? It would be tremendously helpful (for us visual learners) to have a diagram that helps track the studies and publications. **The numbers have been reviewed and corrected and Figure 1 (a flow diagram) has been added.** 5. Page 7: "…as was the time period between granting and fulfillment of the NOC/c." Are there not instances when Health Canada required submission of confirmatory by a certain time to fulfill the NOC/c? Was this information considered by the author? **Only one of the NOC/c reviewed specified a specific date for the submission of the confirmatory studies and this is**

	mentioned in the Results section . 6. Page 8: "The mean length of time between receipt of a NOC/c and fulfillment was 1390 days…" Since the qualifying notices listed between one and seven confirmatory studies, would it be worth breaking down the time between receipt of NOC/c and fulfillment according to the number of confirmatory studies requested? **I am not sure what value this additional analysis would add and therefore I did not undertake it.** 7. Page 9: "… none included a clinicaltrials.gov ID for the study." Earlier in the same paragraph, the author provided an example of a description of the confirmatory studies as follows: "… Final study report of the clinical trial NCT00179621… " Is that a hypothetical example, or a real example? If the latter, it appears to be contradictory to the statement that clinicaltrials.gov ID were not provided. **I thank the reviewer for pointing out this discrepancy and the statement has been changed to say that one QN used a clinicaltrials.gov ID for one study.** 8. Page 9: "In 1 case (dasatinib) one publication was independently identified." Can the author clarify what independent identification means? **The statement has been changed to say that one publication was identified through the database search but was not confirmed by the company.** 9. Page 10: "Most of the confirmatory studies were eventually published…" If I interpreted the numbers correctly, of the 61 confirmatory studies, only 30 published studies (represented in 28 publications) were truly confirmed as matches. Twenty published studies (represented in 19 publications) were likely matches, but there is no absolute certainty, since there was no company response or publication was not confirmed by the companies. Given this, should there be a qualifier placed in this and other similar sentences throughout the manuscript to differentiate the confirmed publications and the likely publications? **The appropriate caveat has been added.** 10. Page 11: "Since the studies were used to fulfill the requirements of the NOC/c, it is highly likely that they were favourable and therefore negative results are probably not an explanation." Are all confirmatory studies required to be "favourable" to fulfil the requirements of the NOC/c? In other words, is it not plausible that some of those studies that may have not been published were "unfavourable" if there were other "favourable" studies submitted? **The reviewer's assumption is plausible but there is no way of determining its accuracy.** 11. Page 12: "From the inception of this pathway in 2006 until April 2014 there were 21 medicines approved requiring 59 confirmatory studies that were expected to take 575 days…" What does the author mean by "expected" to take 575 days? Is there a date by which the studies were required to be completed? Does the expectation refer to the date of completing the studies or the date of re-filing the submission with the regulator? **The studies were on average expected to take 575 days to complete. This point has been clarified.** 12. Page 12: "Studies required by Health Canada take 540 days (1390 – (575 + 275)) longer than those required by the EMA." The author needs to qualify this statement by adding in the fact that the medians are being compared. Also, and this is the bigger point, to what degree is this an appropriate comparison when the drugs under review may be completely different under the two regulators? It would be more appropriate to compare the time to fulfill an NOC/c for the same drugs. I fear this statement could be taken out of context and lead to a misinterpretation that Health Canada takes longer (in general) to fulfil NOC/c when that might not be true. **I thank the reviewer for pointing out that a mean was being compared to a median and have deleted the relevant sentence.** **The paper by Hoekman did not give the time to fulfillment for individual drugs. This point has been added to the manuscript. In addition, there were only 4 drugs in common so any comparisons, if they were possible, would be based on an extremely small sample size.** 13. Page 12: "Additional publications may exist and the ones that were independently found may not be the correct ones." This is a concern I had as well. What assurance, if any, can the author provide about the accuracy of the captured studies? Are there some studies for which the author was more confident than others? Would having a second reviewer to seek the studies have helped? **When published studies were identified by a database search as opposed to being confirmed by the company there was always some degree of uncertainty that it was the correct publication. There is no way of quantifying the degree of uncertainty.** 14. Page 13: "Health Canada and the manufacturer should jointly take responsibility for ensuring that clinicians are aware of the preliminary nature of the evidence for the product and the details of the confirmatory studies that are required." What specific strategies does the author propose to facilitate greater dissemination of said topic? **Information has been added about communication methods – e.g., posting on web sites, "Dear Doctor" letters, information in promotional material.**
Reviewer 3	Dr. Karen Lee MA
Institution	Canadian Agency for Drugs and Technologies in Health, Ottawa, Ont.
General comments (author response in bold)	This is an interesting piece providing some details on the evidence generation and transparency of drugs receiving NOC/c. Overall the major comment is the need to provide more information on the relevance of this issue. 1. In terms of background, it would be helpful for the reader to have some details on the relevance of seeing confirmatory studies. As mentioned by the author, physicians may not be award that a marketed drug has only received NOC/c, and further the conditions may not be known. Are there examples that the author could cite that given the information in provided in confirmatory studies that this might change clinical practice? This would add importance to the issue being presented. **The primary aim of the study was to look at publication rates not the quality of the information in the published studies. Evaluating the information in the studies in such a wide range of drugs would require the expertise of**

	clinicians in multiple areas and is beyond the resources available. 2. Recommendations on what the author feels could address the issues highlighted by the analysis would strengthen this article. **See the response to point 14 from Reviewer 2.** Other comments: 2. Might include a bit more information in the Abstract methods - what period being considered, only efficacy being considered. **These points were added to the Abstract.** 3. In the Background, might be of interest to indicate if there were NOC/c drugs where NOC was revoked either based on lack of confirmatory findings, etc. **This is an interesting point but was outside of the objective of this study.** 4. The measure of 'journal publication' relies on the manufacturer to submit for publication but also for the journal to accept the manuscript. As the confirmatory studies are for Canadian market authorization the potentially relevant journals may be reduced. Where the original study was already published, a confirmatory study may be less attractive to journals. It would be worthwhile for the author to discuss other recommendations/options to have this information publicly available and in a timely manner. **Although the studies were for Health Canada they were not necessarily done in Canada and therefore would not necessarily have been submitted to Canadian journals. In fact, none of the studies either confirmed by the companies nor identified through database searches were published in Canadian journals.** 5. What are the aspects of published confirmatory studies analysed that could influence clinical practice? Teasing this out might allow for the reader to better understand why we should expect to have the results of these studies available **The primary aim of this study was to look at publication rates and not to evaluate the information in the published studies. Evaluating the information in the studies in such a wide range of drugs would require the expertise of clinicians in multiple areas and is beyond the resources available.**