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)	Quality of evidence considered by Health Canada in granting full market authorization to new drugs with a conditional approval: a retrospective cohort study
AUTHORS	Lexchin, Joel

VERSION 1 – REVIEW

REVIEWER	Sumimasa Nagai The University of Tokyo
REVIEW RETURNED	28-Nov-2017

GENERAL COMMENTS	General comments: Although the theme of this study is unique and interesting, conclusions are unclear. Did the author mean that restricted information released by Health Canada are the biggest issues? Or did the author mean that poor quality of evidence used for fulfilling the NOC/c conditions is the biggest issue? The author should clarify. In addition, comparison between different therapeutic areas is not clinically meaningful. Comparison between drugs with a NOC/c that fulfilled the conditions and drugs that were directly granted a full NOC for similar therapeutic areas is more important. The author should make such comparisons. Specific comments: Line 147: What are "two areas"? Line 148: The author should define what endpoints are "surrogate". The author should disclose the primary endpoint in each study in Supplemantary FIle 1. Table 2: Dabrafenib is not used for "multiple myeloma". The author should correct this error.

REVIEWER	Huseyin Naci London School of Economics and Political Science, UK
REVIEW RETURNED	14-Dec-2017

GENERAL COMMENTS	RE: Quality of evidence considered by Health Canada in granting full market authorization to new drugs: a retrospective cohort study In this article, Joel Lexchin reviews the characteristics of the clinical studies that supported Health Canada's decisions on marketing authorizations of new drugs. This article addresses an important question, is well executed, and is reported in a balanced manner. I

	would recommend publishing this paper with minor revisions. I outline my suggestions for minor revisions below. First, the context in which the study was conducted could be described in more detail. Although the author refers to several previous studies evaluating this regulatory pathway, it would be helpful for the reader to understand the proportion of marketing authorizations that receive a 'conditional' Notice of Compliance on the basis of limited evidence. Are there similarities with FDA's expedited approval pathways beyond the requirement for conducting confirmatory studies? For example, can Health Canada withdraw a product from the market if the required confirmatory studies are not completed by a certain deadline? What would be potential implications of demonstrating lack of efficacy in required confirmatory studies? The introduction section of the paper could benefit from a more thorough overview of the policy context with answers to these questions. Second, the methods section could benefit from further detail. In particular, the typology used to categorize outcomes as clinical vs. surrogate should be defined. Third, additional context for interpreting the results could tremendously help with understanding the significance of the findings. For instance, it would be helpful to more clearly report the total number of agents that received 'conditional' Notice of Compliance during the study period, the proportion of required studies by the end of the study, and any deviations from the planned designs and outcomes. Fourth, the sponsor survey is an important strength of the study design and methodology. However, it would be helpful to report the proportion of completed studies that could be identified without a response from the sponsor company. The large number of studies that could not be identified suggests that the information available from the Qualifying Notice reports is inadequate. This limitation should be addressed in the discussion section of the paper with reflections on how this could potentially bias the findings. Fifth, I wonder if it would be possible to comment on (1) whether and (2) the degree to which the completed confirmatory trials may have deviated from the original requirements by Health Canada. Are available data from Health Canada's description adequate to at least partially investigate this question? On a minor point, the abstract could be improved with further detail about the study period. In addition, the focus of the research on 'conditional' approvals could be highlighted in both the title and abstract.

REVIEWER	Jarno Hoekman Utrecht University, The Netherlands
REVIEW RETURNED	24-Jan-2018

GENERAL COMMENTS	This is a well-written paper that gives a relevant overview of the quality of evidence of confirmatory studies conducted under the NOC/c pathway of Health Canada. I have a number of comments. The first two paragraphs in the introduction do not seem to match. The first paragraph starts with a problem statement on the difficulty

	to obtain information on evidence for 'standard' approval decisions by Health Canada. The second paragraph makes a statement that one source for gaining a partial understanding into the quality of evidence are confirmatory studies under the NOC/c pathway. Following this statement I would expect that this information is available from the authorities, but the author instead decides to extract the information from publication sources. This needs to be made explicit, e.g. does the opportunity to conduct the study follow from the fact that study descriptions are available under NOC/c that can provide a starting point for an analysis. The analysis of publication rates is limited and this is a main limitation of the paper. Table 1 does not list the number of required studies for each drug-indication pair (Table 2 does). It might therefore well be that some evidence from studies is not published at all or that some publications report on several required studies at the same time. It would be important to add the number of required studies to Table 1, to establish a more precise match between required studies and publications by linking study goals (from descriptions) with the reported evidence (from publications) and to perform an analyses of the type of studies that are and are not reported in publications. Moreover an analysis of time to publication would be relevant to see when generated evidence becomes publicly available. Finally, it might be interesting to conduct an analysis of the publications that were found but remained unconfirmed by companies. Table 3 could benefit from reporting of proportions. The included drug-indication pairs have been approved over a relatively long period. Are there any time-trends in the data with regard to the quality of evidence? It would interesting to know whether the conclusion regarding age and sex of trial participants are specific for confirmatory studies conducted under the NOC/c pathway or a more general characteristic of drug approvals. One of the main conclusions is not adequately reflected in the abstract: "studies required by Health Canada had more rigorous methodology than those required by either the FDA or the EMA". The last paragraph in the conclusion reflects on transparency. It would be important to be precise here about how transparency of the authorities could be improved both with regard to drugs approved under standard and NOC/c pathway. The analysis is about the latter, the statements seem to be more about the former. Moreover, the statements are somewhat normative. Although I understand the importance of transparency, the reasons to pursue this goal are not made explicit in the article. It might also be interesting to mention why steps towards transparency have not yet been taken by Health Canada or why they were not successful so far.

VERSION 1 – AUTHOR RESPONSE

February 20, 2018

To The Editor:

Thank you for your comments and those of the reviewers. Below in italics I have indicated how I responded to those comments. In addition to making the requested changes computational and transcription errors have also been corrected.

Comments from the Associate Editor:

A bit of explaining is needed:

* Can they start by explaining what Health Canada is and its role.

An opening paragraph has been added to explain that Health Canada fulfills the same role in regulating drugs as the Food and Drug Administration and the European Medicines Agency and provides a basic description of how it operates.

* It might be helpful if the author provided a chart/ diagram explaining the regulatory pathway.

The primary purpose of this paper is to evaluate the quality of the evidence that Health Canada uses to make a decision about whether to allow a product on the market and not the regulatory pathways that it uses. I think that comparing Health Canada to the FDA and the EMA should provide sufficient information to readers without the need to add a chart or diagram.

Reviewer: 1

Reviewer Name: Sumimasa Nagai

General comments:

Although the theme of this study is unique and interesting, conclusions are unclear.

Did the author mean that restricted information released by Health Canada are the biggest issues?

Or did the author mean that poor quality of evidence used for fulfilling the NOC/c conditions is the biggest issue?

The author should clarify.

The Conclusion already states that the concern is the quality of the evidence and a sentence has been added to the end of the first paragraph in the Discussion that also makes this point.

In addition, comparison between different therapeutic areas is not clinically meaningful.

Comparison between drugs with a NOC/c that fulfilled the conditions and drugs that were directly granted a full NOC for similar therapeutic areas is more important.

The author should make such comparisons.

The reviewer makes a good point but as I indicated in the Introduction Health Canada does not release enough information about drugs that go through the regular NOC approval process to be able to identify publications related to the trials that the companies undertook. A sentence has been added to the end of the second paragraph in the Introduction to make this point clearer.

Specific comments:

Line 147: What are "two areas"?

The wording in this sentence has been changed to clarify this point.

Line 148: The author should define what endpoints are "surrogate". The author should disclose the primary endpoint in each study in Supplementary File 1.

The manuscript now contains the definition of surrogate and clinical. A column has been added to Supplementary File 1 giving the primary endpoint for each study.

Table 2: Dabrafenib is not used for "multiple myeloma". The author should correct this error.

The error has been corrected.

Reviewer: 2

Reviewer Name: Huseyin Naci

In this article, Joel Lexchin reviews the characteristics of the clinical studies that supported Health Canada's decisions on marketing authorizations of new drugs. This article addresses an important question, is well executed, and is reported in a balanced manner. I would recommend publishing this paper with minor revisions. I outline my suggestions for minor revisions below.

I thank the reviewer for the compliment.

First, the context in which the study was conducted could be described in more detail. Although the author refers to several previous studies evaluating this regulatory pathway, it would be helpful for the reader to understand the proportion of marketing authorizations that receive a 'conditional' Notice of Compliance on the basis of limited evidence. Are there similarities with FDA's expedited approval pathways beyond the requirement for conducting confirmatory studies? For example, can Health Canada withdraw a product from the market if the required confirmatory studies are not completed by a certain deadline? What would be potential implications of demonstrating lack of efficacy in required confirmatory studies? The introduction section of the paper could benefit from a more thorough overview of the policy context with answers to these questions.

It is now noted that Health Canada's NOC/c policy is similar to the FDA's accelerated approval process and that should the postmarket studies not confirm the efficacy of a drug that the drug could be removed from the market.

Information about the total number of NOC/c issued and a percent of all new drug approvals is now in the Results section.

Second, the methods section could benefit from further detail. In particular, the typology used to categorize outcomes as clinical vs. surrogate should be defined.

A definition of surrogate and clinical outcomes is now given in the Methods.

Third, additional context for interpreting the results could tremendously help with understanding the significance of the findings. For instance, it would be helpful to more clearly report the total number of agents that received 'conditional' Notice of Compliance during the study period, the proportion of required studies by the end of the study, and any deviations from the planned designs and outcomes.

The start of the Results now gives the total number of products (and indications) that received a NOC/c. I am not sure what the reviewer means by "the proportion of required studies by the end of the study period" but if he could clarify what he is asking for I could insert the necessary data. Unfortunately there is no publicly available information to determine if there were deviations from the planned designs and outcomes.

Fourth, the sponsor survey is an important strength of the study design and methodology. However, it would be helpful to report the proportion of completed studies that could be identified without a response from the sponsor company. The large number of studies that could not be identified suggests that the information available from the Qualifying Notice reports is inadequate. This limitation should be addressed in the discussion section of the paper with reflections on how this could potentially bias the findings.

The sponsor survey was undertaken because the limited information in the Qualifying Notices generally made it impossible to be certain if the correct publication was identified. Therefore, it is not possible to comply with the reviewer's suggestion to report on the proportion of completed studies that could be identified without a company response.

The Methods already notes the variability of information in the Qualifying Notices about the required studies: "Descriptions of the required studies in the QNs were highly variable ranging from e.g., "data from the extension studies 105E2, 106E1" to quite detailed, e.g., "Study TMC435HPC3017 (planned N=300): A Phase III, multicenter, randomized, open label study to investigate the efficacy and safety of a 12- or 8-week treatment regimen of simeprevir in combination with sofosbuvir in treatment-naïve and -experienced subjects with chronic genotype 1 HCV infection without cirrhosis."

The following has now been inserted in the Limitations: Had the Qualifying Notices issued by Health Canada contained more detailed information about the required postmarket studies it may have been possible to identify more publications even without a response from the companies."

Fifth, I wonder if it would be possible to comment on (1) whether and (2) the degree to which the completed confirmatory trials may have deviated from the original requirements by Health Canada. Are available data from Health Canada's description adequate to at least partially investigate this question?

There is no information available to be able to answer this question.

On a minor point, the abstract could be improved with further detail about the study period. In addition, the focus of the research on 'conditional' approvals could be highlighted in both the title and abstract.

The title and the abstract have been changed.

Reviewer: 3

Reviewer Name: Jarno Hoekman

This is a well-written paper that gives a relevant overview of the quality of evidence of confirmatory studies conducted under the NOC/c pathway of Health Canada. I have a number of comments.

I thank the reviewer for the compliment.

The first two paragraphs in the introduction do not seem to match. The first paragraph starts with a problem statement on the difficulty to obtain information on evidence for 'standard' approval decisions by Health Canada. The second paragraph makes a statement that one source for gaining a partial understanding into the quality of evidence are confirmatory studies under the NOC/c pathway. Following this statement I would expect that this information is available from the authorities, but the author instead decides to extract the information from publication sources. This needs to be made explicit, e.g. does the opportunity to conduct the study follow from the fact that study descriptions are available under NOC/c that can provide a starting point for an analysis.

It is now made clear that Health Canada does not release any clinical trial information in order to analyze its quality and that is why it is necessary to use the postmarket studies required under the NOC/c and link those studies with subsequent publications.

The analysis of publication rates is limited and this is a main limitation of the paper. Table 1 does not list the number of required studies for each drug-indication pair (Table 2 does). It might therefore well be that some evidence from studies is not published at all or that some publications report on several required studies at the same time. It would be important to add the number of required studies to Table 1, to establish a more precise match between required studies and publications by linking study goals (from descriptions) with the reported evidence (from publications) and to perform an analyses of the type of studies that are and are not reported in publications. Moreover an analysis of time to publication would be relevant to see when generated evidence becomes publicly available. Finally, it might be interesting to conduct an analysis of the publications that were found but remained unconfirmed by

companies.

A column has been added to Table 1 giving the number of required studies listed in the Qualifying Notices. Out of 40 studies, companies confirmed 37 publications. One company only confirmed a publication for 1 of 3 required studies, in 2 cases 2 studies were combined in a single publication. Therefore, there were only 2 required studies for which publications were not confirmed. Given this small number of unconfirmed studies any analysis would not provide any useful information. A previous publication of mine has already looked at the time of publication for articles based on confirmatory studies and therefore this analysis was not repeated (Lexchin J. Publication of confirmatory studies required by Health Canada for drugs approved under a Notice of Compliance with conditions: a cohort study. CMAJ Open 2017;5:E295-E300).

Table 3 could benefit from reporting of proportions.

Table 3 has been modified to include percentages.

The included drug-indication pairs have been approved over a relatively long period. Are there any time-trends in the data with regard to the quality of evidence?

The NOC/c policy was only revised a single time in February 2003. Up until then only 4 products – abacavir (HIV/AIDS), alteplase (stoke), recombinant factor VIIa (bleeding disorder) and zanamivir (influenza) had received a NOC/c. These products have very different indications and the data shows that the characteristics of the clinical studies for different indications are quite variable. Therefore comparing the characteristics of the studies for these 4 products with those for the products receiving a NOC/c after February 2003 to look for time trends could produce misleading results.

It would interesting to know whether the conclusion regarding age and sex of trial participants are specific for confirmatory studies conducted under the NOC/c pathway or a more general characteristic of drug approvals.

The only other source of data regarding trial characteristics for drugs in general is the Summary Basis of Decision. As I note in the Introduction, the quality of data in these documents is quite variable and therefore it is not possible to compare study characteristics for drugs in general with those approved through the NOC/c policy.

One of the main conclusions is not adequately reflected in the abstract: “studies required by Health Canada had more rigorous methodology than those required by either the FDA or the EMA”.

The abstract has been modified.

The last paragraph in the conclusion reflects on transparency. It would be important to be precise here about how transparency of the authorities could be improved both with regard to drugs approved under standard and NOC/c pathway. The analysis is about the latter, the statements seem to be more about the former. Moreover, the statements are somewhat normative. Although I understand the importance of transparency, the reasons to pursue this goal are not made explicit in the article. It might also be interesting to mention why steps towards transparency have not yet been taken by Health Canada or why they were not successful so far.

The paragraph in question has been modified to emphasize that Health Canada is currently developing regulations that will result in the public release of all of the safety and efficacy data once a drug has been approved for marketing.

Sincerely,

Joel Lexchin

VERSION 2 – REVIEW

REVIEWER	Sumimasa Nagai The University of Tokyo, JAPAN

REVIEW RETURNED	25-Feb-2018

GENERAL COMMENTS	None

REVIEWER	Huseyin Naci London School of Economics, UK
REVIEW RETURNED	10-Mar-2018

GENERAL COMMENTS	The author has effectively addressed all of my comments. Many thanks.

REVIEWER	Jarno Hoekman Utrecht University, The Netherlands
REVIEW RETURNED	11-Mar-2018

GENERAL COMMENTS	The author has adequately addressed my comments. Please carefully check the final version for spelling mistakes, e.g.: line 71: substitute "," with "." line 78: "makes" instead of "make" line 79: "issues" instead of "issue" line 100-104: sentence needs to be refomulated