PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Health Canada's use of expedited review pathways and therapeutic innovation, 1995-2016: cross sectional analysis
AUTHORS	Lexchin, Joel

VERSION 1 – REVIEW

REVIEWER	Jonathan J. Darow Harvard Medical School, United States
REVIEW RETURNED	29-Apr-2018

GENERAL COMMENTS	TITLE: The author might consider replacing "accelerated review pathways" with "expedited review"; in the US, "accelerated approval" refers to a specific program (as does "accelerated assessment" in the EU), so its alternate use in the title could cause confusion among some readers. Page 3 line 46: Clarify the relationship between the total number of drugs and the percents, e.g., "Of [623?] drugs approved by Health Canada between 1995 and 2016, 438 (70.3%) followed the standard pathway while 185 (29.7%)…" Clarify whether all 55 "innovative" drugs received accelerated approval, or whether some number of these received standard review (same comment for page 13 line 231). Clarify what the Kappa value measures (in this context), e.g., "…indicating fair agreement between X and Y." Page 5 line 67: Rephrase to replace "get" with "obtain"/"secure" or similar, e.g., "In order to obtain authorization to market an NAS in Canada, …" Add comma after "(NDS)," and after "quality" Page 5 line 76: delete "can" Page 5 line 89: It may be helpful to clarify quantitatively how readers should interpret Kappa. For example, is the theoretical maximum "1," indicating perfect agreement? Or, is 1.2 the max (as suggested by Figure 2)? This could be discussed further, for example, at page 9 lines 164-66. Page 6 line 112: Rephrase so the sentence does not begin with the year "1995," e.g., "A starting date of 1995 was selected…" Page 7 line 122-23: Rephrase to clarify. If you are considering only NAS, it is not clear what you mean by "drugs approved for the first time…." Page 7 line 131: "therapeutically innovation" □ "therapeutic innovation"? Page 8 line 142: Sentence beginning "If a drug…" and the following sentence appear to be redundant. If not, clarify the difference. Page 9 line 164: Clarify what is meant by "were combined." Did you create two categories? I.e.: (1) drugs given standard review; and (2) drugs receiving priority review, NOC/c, or both. If so, can this be stated more clearly? Page 10 line 176: Give the second-level ATC codes corresponding to the 3 groups you mention.

	Page 10 line 197: Remove the second % character in: "%%" Page 12 line 217: "(n=67)" ? Page 12 line 218: "significantly different" □ consider clarifying *how* the groups were different Page 15 line 248: Be consistent with either "biologics" or "biologicals" Page 16 line 266: Do you mean "at least one"? Page 16 line 278: From table 4, a reader cannot tell whether all drugs rated as innovative by Prescrire/PMPRB received accelerated review. In other words, did the two groups represent two overlapping circles, or one smaller "innovative drug" circle within a larger "accelerated review" circle. If the latter is the case, then is it not possible that Prescrire/PMPRB simply have a higher threshold for innovativeness than Health Canada? And if that is the case, would the Kappa reflect not poor agreement, but simply a different threshold (perhaps intentionally erring on the side of expediting review)? From Supplement 1, it appears at least some drugs received an "innovative" rating by Prescrire/PMPRB and also received standard review by Health Canada, but unless one is prepared to count, it is not immediately obvious how often this occurred. Consider revising Table 4 to clarify this issue. The issue is important because the conclusion of poor agreement will be stronger if an appreciable number of the drugs rated as "innovative" were NOT given expedited review. For similar reasons, when you suggest Health Canada "seems somewhat better at predicting the therapeutic value of drugs in the 'all other therapeutic groups' than it does for drugs in the antineoplastic, antiviral and immunosuppressant groups" could this not be simply because Health Canada is more generous in expediting the review of drugs in the latter categories? (You suggest this earlier, at page 16 line 273). Similarly, the reference on Page 18 line 320 to Health Canada's "encouraging" performance with respect to certain categories may simply reflect the fact that it is not as generous with those groups, not that its performance is more accurate. But it is difficult to assess based on the current manuscript. Page 17 line 285: Not sure what you mean by "how Health Canada evaluates therapeutic value." Does it make an assessment separate from priority/NOC/c? Page 18 line 326: You earlier describe NOC/c as "Phase II clinical trials or trials with only surrogate markers." If that is the case, then NOC/c combines features of the US Fast Track and Accelerated Approval programs. Consider softening the term "equivalent," e.g., "which approximately corresponds to" etc. Page 18 line 332: Consider changing "neoplastic" to "antineoplastic" Page 19 line 335: Is the comparison to Europe an apples-to-apples comparison? The cited source (Boon; see Figure 1), appears to report only conditional approvals and exceptional circumstances, but not accelerated assessment, which is most closely analogous to priority review. Page 19 line 349: change to "use of these pathways comes…" Supplementary table 1: The header to column 3 appears to be truncated. The final line of the table also appears to be truncated.

REVIEWER	Alex Faulkner University of Sussex, UK
REVIEW RETURNED	27-May-2018

GENERAL COMMENTS	A strong paper based on robust analysis, with convincing conclusions. The findings are important not only for Health Canada, but other regulatory regimes where use of conditional approval is

	high or even increasing in specific applications e.g. 'regenerative' medicines. A few minor comments/suggestions : - at line 57 the Summary/Limitations consists of summary points, not Strengths/Limitations as the subhead would suggest. -in the Abstract 'relatively poor' - relative to what? - surely just 'poor' is justified here. - Methods - a brief indication of how data were extracted from Annual Reports - manually? by the author? etc. -line 131 - 'therapeutically innovation' - innovative. - line 335 EMA = European Medicines Agency, not 'Association'. - Other limitations could be suggested? - Conclusion: could suggest the potential importance of the analysis for other regimes - USA, EU (Early Access to Medicines initiative), Japan...Why has Canada's use of accelerated review remained stable while others are increasing?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

TITLE: The author might consider replacing “accelerated review pathways” with “expedited review”; in the US, “accelerated approval” refers to a specific program (as does “accelerated assessment” in the EU), so its alternate use in the title could cause confusion among some readers.

The title has been changed as outlined above under the response to the editors. In addition, the word “accelerated” has been replaced with “expedited” throughout the manuscript.

Page 3 line 46: Clarify the relationship between the total number of drugs and the percents, e.g., “Of [623?] drugs approved by Health Canada between 1995 and 2016, 438 (70.3%) followed the standard pathway while 185 (29.7%)…” Clarify whether all 55 “innovative” drugs received accelerated approval, or whether some number of these received standard review (same comment for page 13 line 231). Clarify what the Kappa value measures (in this context), e.g., “…indicating fair agreement between X and Y.”

The sentence now starts “Of 623 drugs approved by Health Canada between 1995 and 2016…”

The following sentence has been added to both the abstract (line 48 in the original manuscript): and the main text (line 231 in the original manuscript):

“Forty-two of the 55 therapeutically innovative drugs received an expedited review and 13 received a standard review.”

The following phrase has been added to clarify the meaning of the Kappa value: "indicating "fair" agreement between Health Canada's use of expedited pathways and independent evaluations of therapeutic innovation."

Page 5 line 67: Rephrase to replace "get" with "obtain"/"secure" or similar, e.g., "In order to obtain authorization to market an NAS in Canada, …" Add comma after "(NDS)," and after "quality"

The sentence has now been reworded to read "In order to obtain authorization to market a new active substance…"

Page 5 line 76: delete "can"

The word "can" has been deleted.

Page 5 line 89: It may be helpful to clarify quantitatively how readers should interpret Kappa. For example, is the theoretical maximum "1," indicating perfect agreement? Or, is 1.2 the max (as suggested by Figure 2)? This could be discussed further, for example, at page 9 lines 164-66.

The meaning of the different Kappa values has been added on lines 187-190 of the revised manuscript.

Page 6 line 112: Rephrase so the sentence does not begin with the year "1995," e.g., "A starting date of 1995 was selected…"

The start of the sentence has been changed to "A starting year of 1995 was selected…"

Page 7 line 122-23: Rephrase to clarify. If you are considering only NAS, it is not clear what you mean by "drugs approved for the first time…."

The word "drugs" has been replaced by "NAS".

Page 7 line 131: "therapeutically innovation" □ "therapeutic innovation"?

"Therapeutic innovation" has been substituted for "therapeutically innovation".

Page 8 line 142: Sentence beginning “If a drug…” and the following sentence appear to be redundant. If not, clarify the difference.

The sentence on line 142 of the original manuscript beginning “If a drug…” has been deleted and the following sentence modified to read “If both the PMPRB and Prescrire…”

Page 9 line 164: Clarify what is meant by “were combined.” Did you create two categories? I.e.: (1) drugs given standard review; and (2) drugs receiving priority review, NOC/c, or both. If so, can this be stated more clearly?

The sentence starting “Owing to the small…” has been replaced by “Drugs approved through the priority review and NOC/c pathways were analyzed together as a single group.”

Page 10 line 176: Give the second-level ATC codes corresponding to the 3 groups you mention.

The second level ATC codes have been added.

Page 10 line 197: Remove the second % character in: “%%”

The extra % has been removed.

Page 12 line 217: “(n=67)” ?

The number should be 68 not 67. It has been made clear that the n=68 applies to the other therapeutic groups, i.e., besides the three that were analyzed the rest of the drugs were in 68 different second-level therapeutic groups.

Page 12 line 218: “significantly different” □ consider clarifying *how* the groups were different

Table 3 gives the distribution of the groups by review pathways and I do not believe that any further clarification is needed in the text.

Page 15 line 248: Be consistent with either “biologics” or “biologicals”

"Biologics" is now consistently used.

Page 16 line 266: Do you mean "at least one"?

The wording has been changed to "at least one".

Page 16 line 278: From table 4, a reader cannot tell whether all drugs rated as innovative by Prescrire/PMPRB received accelerated review. In other words, did the two groups represent two overlapping circles, or one smaller "innovative drug" circle within a larger "accelerated review" circle. If the latter is the case, then is it not possible that Prescrire/PMPRB simply have a higher threshold for innovativeness than Health Canada? And if that is the case, would the Kappa reflect not poor agreement, but simply a different threshold (perhaps intentionally erring on the side of expediting review)? From Supplement 1, it appears at least some drugs received an "innovative" rating by Prescrire/PMPRB and also received standard review by Health Canada, but unless one is prepared to count, it is not immediately obvious how often this occurred. Consider revising Table 4 to clarify this issue. The issue is important because the conclusion of poor agreement will be stronger if an appreciable number of the drugs rated as "innovative" were NOT given expedited review. For similar reasons, when you suggest Health Canada "seems somewhat better at predicting the therapeutic value of drugs in the 'all other therapeutic groups' than it does for drugs in the antineoplastic, antiviral and immunosuppressant groups" could this not be simply because Health Canada is more generous in expediting the review of drugs in the latter categories? (You suggest this earlier, at page 16 line 273). Similarly, the reference on Page 18 line 320 to Health Canada's "encouraging" performance with respect to certain categories may simply reflect the fact that it is not as generous with those groups, not that its performance is more accurate. But it is difficult to assess based on the current manuscript.

An extra column has been added to Table 4 showing the number of therapeutically innovative NAS that received a priority review in each year. In addition, the following sentence was added based on the reviewer's comment: "Furthermore, almost 25% (13/55) of the drugs that were therapeutic innovations did not receive an expedited review underscoring that Health Canada is not reliably able to predict which drugs will offer major therapeutic gains."

The reviewer suggests that Health Canada may be more generous towards drugs in "all other therapeutic groups" as a reason for a better Kappa score. However, it is more likely that Health Canada views drugs in these groups to be less likely to be therapeutic innovations. In support of this position on lines 316-318 of the revised manuscript I added the sentence "Drugs in the three therapeutic subgroups were much less likely to receive a standard review than were drugs in "all other therapeutic groups", 43.7% versus 79.3% (data not shown)." and on lines 354-358 of the revised manuscript the following was added: "This difference may because Health Canada is better able to predict these drugs are less likely to be therapeutic innovations than drugs in the antineoplastic, antiviral and immunosuppressant groups. Out of the 357 drugs that had therapeutic evaluations in the "all other therapeutic groups," 79.3% received a standard review compared to 43.7% of the 151 drugs in the three therapeutic subgroups."

The sentence on lines 318-320 of the original manuscript has been deleted: "The fact that it appears to be better at predicting therapeutic innovation for some therapeutic subgroups is encouraging."

Page 17 line 285: Not sure what you mean by "how Health Canada evaluates therapeutic value."

Does it make an assessment separate from priority/NOC/c?

The word "evaluates" has been replaced by "predicts".

Page 18 line 326: You earlier describe NOC/c as "Phase II clinical trials or trials with only surrogate markers." If that is the case, then NOC/c combines features of the US Fast Track and Accelerated Approval programs. Consider softening the term "equivalent," e.g., "which approximately corresponds to" etc.

The change has been made.

Page 18 line 332: Consider changing "neoplastic" to "antineoplastic"

The change has been made.

Page 19 line 335: Is the comparison to Europe an apples-to-apples comparison? The cited source (Boon; see Figure 1), appears to report only conditional approvals and exceptional circumstances, but not accelerated assessment, which is most closely analogous to priority review.

The reviewer is correct and the sentence on lines 333-336 of the original manuscript has been replaced with the following: "The European Medicines Association (EMA) does not have the equivalent of a priority review but its exceptional conditions (EC) and conditional approvals (CA) pathways are roughly equivalent to a NOC/c. These were used for 12.5% (70/558) new drugs it approved from 1995 to 2009 (18), while Health Canada used a NOC/c for 5.3% (33/623) approvals between 1995 and 2016."

Page 19 line 349: change to "use of these pathways comes…"

The change has been made.

Supplementary table 1: The header to column 3 appears to be truncated. The final line of the table also appears to be truncated.

The table has been reformatted.

Reviewer: 2

A strong paper based on robust analysis, with convincing conclusions. The findings are important not only for Health Canada, but other regulatory regimes where use of conditional approval is high or even increasing in specific applications e.g. 'regenerative' medicines.

I thank the reviewer for his compliment.

A few minor comments/suggestions :

- at line 57 the Summary/Limitations consists of summary points, not Strengths/Limitations as the subhead would suggest.

I have looked at recent articles published in BMJ Open and the Strengths and Limitations in my manuscript seem in line with those in these articles.

-in the Abstract 'relatively poor' - relative to what? - surely just 'poor' is justified here.

The word "relatively" has been deleted.

- Methods - a brief indication of how data were extracted from Annual Reports - manually? by the author? etc.

The part of the sentence on lines 114-115 of the original manuscript has been revised to read: "were manually extracted from the annual reports by the author."

-line 131 - 'therapeutically innovation' - innovative.

As per the response to reviewer 1, this has been changed to "therapeutic innovation".

- line 335 EMA = European Medicines Agency, not 'Association'.

“Association” has been changed to “Agency”.

- Other limitations could be suggested?

The following has been added to the Limitations: “The lack of the availability of reports from Health Canada reviewers means that the reasons why drugs were assigned to a specific review pathway cannot be evaluated.”

- Conclusion: could suggest the potential importance of the analysis for other regimes - USA, EU (Early Access to Medicines initiative), Japan...Why has Canada's use of accelerated review remained stable while others are increasing?

The following sentence was added to the Conclusion: “Other regulatory authorities such as the Australian Therapeutic Goods Administration and the EMA are in the process of either implementing or expanding expedited review pathways (19-21) and should study the example of what has happened in Canada.”

At present, the only other analysis of expedited review pathways comes from the United States. Exploring why the FDA has increased its use of these pathways while Canada has not would involve a detailed discussion about all aspects of regulatory culture which is beyond the scope of this paper.

FORMATTING AMENDMENTS

- Please remove all your figures in your main document and upload each of them separately under file designation ‘Image' (except tables and please ensure that Figures are of better quality or not pix-elated when zoom in). NOTE: They can be in TIFF or JPG format and make sure that they have a resolution of at least 300 dpi and at least 90mm x 90mm of width. Figures in PDF, DOCUMENT, EXCEL and POWER POINT format are not acceptable.

The figures have been removed from the main document and have been uploaded as TIFF files under the designation “Image”.

- Please include Figure legends at the end of your main manuscript.

Figure legends now appear at the end of the manuscript.

- Kindly re-upload supplementary table 2 in PDF format.

Supplementary table 2 has been re-uploaded in PDF format.

VERSION 2 – REVIEW

REVIEWER	Jonathan Darrow Harvard University
REVIEW RETURNED	22-Jun-2018

GENERAL COMMENTS	This work contributes an important insight: In Canada, the concordance between drugs deserving of expedited review and those receiving it is poor. - The reviewer provided a marked copy with comments. Please contact the publisher for full details.

VERSION 2 – AUTHOR RESPONSE

Thank you to the reviewer for the additional comments. Below I indicate how I responded to them. The line numbers refer to those in the version containing the reviewer's comments.

Lines 36-37: The font has been corrected.

Line 54: The sentence now reads "It was unable to reliably predict which drugs will offer major therapeutic gains."

Table 1: The section highlighted by the reviewer has been deleted.

Line 204-205: The part of the sentence now reads "and the review status and therapeutic ratings were compared for each drug in each of the subgroups including "all other therapeutic groups" and Kappa values were calculated for each subgroup."

Line 224: It is now noted that Figure 1 was assessed based on visual inspection.

Line 285: It is now stated that the 95% CI for the immunosuppressant group overlaps with the “all other therapeutic groups”.

Lines 288 and 299: The figures have been changed to 79.1% and 20.9%.

Lines 362-367: The similarity between the EMA’s accelerated assessment and Health Canada’s priority review is now noted and the reference to the exceptional circumstances pathway has been removed. In addition, the numbers have been updated. The sentence now reads “The accelerated assessment (AA) process and the conditional approvals pathway used by the European Medicines Agency (EMA) are roughly the equivalent of Health Canada’s priority review and NOC/c pathway 18. The EMA used the former for 15.5% (23/148) of new drugs between 2012 and 2016 19 20, while the latter was used for 10.1% (30/296) of new drugs between 2006 and 2016 20 21. In the same time periods, Health Canada used a priority approval 21.6% (35/162) of the time time and its NOC/c pathway 9.1% (28/308) of the time.”

Finally, all of the minor copyediting changes suggested by the reviewer have been made.