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)	Health Canada's Use of its Priority Review Process for New Drugs: A Cohort Study
AUTHORS	Lexchin, Joel

VERSION 1 - REVIEW

REVIEWER	Shobha Phansalkar USA
REVIEW RETURNED	13-Jan-2015

GENERAL COMMENTS	Abstract Objectives 1. Compare Health Canada's use of priority reviews to therapeutic ratings between by the 2. Objectives need to explain why this comparison is important? 3. What makes the reviews/ ratings assigned by Precrire/ PMPRB better/ Why should Health Canada change its priority ratings because there is low agreement with these ratings? 4. Some introduction to what is different between the ratings should be provided in the abstract early on, such as in this sentence, "Compares premarket priority review status from Health Canada to postmarket therapeutic status as assessed by two independent organizations" 5. And that for the purposes of this study the author is considering postmarket therapeutic assessment as the gold standard 6. Consider re-writing the Abstract with these recommendations and to make it easier for the reader to follow the premise of this study. Introduction: 7. The purpose of this study is to investigate whether granting a drug a priority status review predicts its therapeutic value once it is marketed. The author has used two types of ratings to determine this—priority ratings from Health Canada and post market therapeutic value ratings from the Canadian Patented Medicine Prices Review Board (PMPRB) and the French drug bulletin Prescrire International. Methods: 8. Data analyses: The methodology is biased towards considering the drugs as innovative. If there was disagreement between Prescrire and PMPRB the drug would still be condiered innovative if ones of the organizations deemed it so. I am interested to know in what % of cases did this happen. The other thing that could have biased readings is only the first year rating was taken into account and not the changed rating over time. A drug could have been determined as innovative when it first enters the market and ratings may have changed thereafter which would be reflected in the subsequent post-market ratings. 9. Do ratings usually change from innovative to non-innovative or the

	other way around? Can the authors comment on whether there is a trend in terms of post market ratings of drugs? 10. Chi square test and kappa values are appropriately employed in the analyses 11. Health Canada's priority review ratings are more generous than the ratings assigned on the innovativeness of the drug post-market. Of note is the negative predictive value of Health Canada's ratings which was 92%. Discussion: 12. One thing that is unclear in my mind is whether the low agreement between the ratings is because the two types of ratings are meant to measure very different things? - Can the authors comment on what the priority ratings from Health Canada measure/ determine? What is this rating based on? - What does the post market "innovative' determination of a drug from PMPRB/ Prescrire really mean? What are the criteria used to assess the same? - If these two types of ratings really are a measure of very different things is it even fair to conduct inter rather agreement? - The authors make note of this on Line 35 Page 13 but I would have wanted this clarification to be made earlier on, perhaps in the Methods section where I was trying to understand why we are comparing these ratings. 13. For all the limitations that the author states about the ratings and how they are different I am not sure the conclusion should be Health Canada should reassess the criteria used for its priority review. Perhaps the concluding remarks should contain a summary of why the author believes this is so.

REVIEWER	Aidan Hollis University of Calgary
REVIEW RETURNED	21-Feb-2015

GENERAL COMMENTS	The author could easily present the data in a much more accessible format, for example in a Venn diagram, or the like, so that we could see the overlap between priority review status, and PMPRB and Prescrire status (perhaps separately). Further, it could indicate whether there is any change in the "accuracy" of priority review status over time. Further, it could reasonably discuss why, given uncertainty, it may be appropriate to grant priority review status, which would lead to many more products receiving priority review than are ultimately identified as innovative etc by Prescrire/PMPRB. I also note that while this article has been 141 days in review, it has spent only 1 day with me.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Shobha Phansalkar

Abstract
Objectives
1. Compare Health Canada's use of priority reviews to therapeutic ratings between
by the

No changes are necessary.

2. Objectives need to explain why this comparison is important?

In the Objectives it is now pointed out that priority reviews are more resource intensive and drugs approved through a priority review are more likely to acquire a serious safety warning.

3. What makes the reviews/ ratings assigned by Precrire/ PMPRB better/ Why
should Health Canada change its priority ratings because there is low agreement
with these ratings?

Unfortunately, due to the word limit for the Abstract, there is no room to include this information but it is included in the Methods section.

4. Some introduction to what is different between the ratings should be provided in
the abstract early on, such as in this sentence, "Compares premarket priority
review status from Health Canada to postmarket therapeutic status as assessed by
two independent organizations"

This change has been made.

5. And that for the purposes of this study the author is considering postmarket
therapeutic assessment as the gold standard

This change has been made.

6. Consider re-writing the Abstract with these recommendations and to make it
easier for the reader to follow the premise of this study.

See the responses to the first five points.

Introduction:
7. The purpose of this study is to investigate whether granting a drug a priority status
review predicts its therapeutic value once it is marketed. The author has used two
types of ratings to determine this—priority ratings from Health Canada and post market therapeutic value ratings from the Canadian Patented Medicine Prices Review Board (PMPRB) and the French drug bulletin Prescrire International.

No changes are necessary.

Methods:
8. Data analyses: The methodology is biased towards considering the drugs as
innovative. If there was disagreement between Prescrire and PMPRB the drug
would still be condiered innovative if ones of the organizations deemed it so. I am

interested to know in what % of cases did this happen. The other thing that could have biased readings is only the first year rating was taken into account and not the changed rating over time. A drug could have been determined as innovative when it first enters the market and ratings may have changed thereafter which would be reflected in the subsequent post-market ratings.

A sensitivity analysis has now been done where the products with discordant ratings – one innovative and one not innovative – have been categorized as not innovative and the Kappa score for the entire 16-year period along with the positive and negative predictive values have been recalculated.

Only Prescrire reassesses the innovation status of products. All products evaluated by Prescrire were searched on the Prescrire web site to determine if a subsequent assessment changed the initial determination of the innovation status. There were no cases where this happened and this is reported in the Results section.

9. Do ratings usually change from innovative to non-innovative or the other way around? Can the authors comment on whether there is a trend in terms of post market ratings of drugs?

See the reply to point 8 above.

10. Chi square test and kappa values are appropriately employed in the analyses

No changes are necessary.

11. Health Canada's priority review ratings are more generous than the ratings assigned on the innovativeness of the drug post-market. Of note is the negative predictive value of Health Canada's ratings which was 92%.

No changes are necessary.

Discussion:

12. One thing that is unclear in my mind is whether the low agreement between the ratings is because the two types of ratings are meant to measure very different things?
- Can the authors comment on what the priority ratings from Health Canada measure/ determine? What is this rating based on?

Beyond the definitions in Table 1, there is no other publicly available information about how Health Canada makes its decision to award a priority review. The lack of any such information is pointed out in the Methods section.

- What does the post market "innovative' determination of a drug from PMPRB/ Prescrire really mean? What are the criteria used to assess the same?
- If these two types of ratings really are a measure of very different things is it even fair to conduct inter rather agreement?
- The authors make note of this on Line 35 Page 13 but I would have wanted this clarification to be made earlier on, perhaps in the Methods section where I was trying to understand why we are comparing these ratings.

The Methods section now gives information about how PMPRB and Prescrire make decisions regarding innovation
.

13. For all the limitations that the author states about the ratings and how they are different I am not sure the conclusion should be Health Canada should reassess the criteria used for its priority review. Perhaps the concluding remarks should contain a summary of why the author believes this is so.

The two points made in the Introduction are restated – first, priority reviews are resource intensive and second, drugs approved through the priority review process are more likely to acquire a serious safety warning.

Reviewer Name Aidan Hollis
Institution and Country University of Calgary
Please state any competing interests or state 'None declared': none declared

The author could easily present the data in a much more accessible format, for example in a Venn diagram, or the like, so that we could see the overlap between priority review status, and PMPRB and Prescrire status (perhaps separately).

The recommendation to use a Venn diagram was considered but I decided to retain the existing tables. The table listing the Kappa values for each of the 16 years would have required 16 separate Venn diagrams.

Further, it could indicate whether there is any change in the "accuracy" of priority review status over time.

I have now added figure 2 giving the Kappa values over the 16-year period. Figure 2 shows that there has not been any temporal change in the accuracy of Health Canada's use of priority reviews.

Further, it could reasonably discuss why, given uncertainty, it may be appropriate to grant priority review status, which would lead to many more products receiving priority review than are ultimately identified as innovative etc by Prescrire/PMPRB.

In the concluding paragraph I have identified a couple of scenarios where priority reviews should continue to be used even in the face of considerable uncertainty about the degree of therapeutic innovation.

Correction

Lexchin J. Health Canada's use of its priority review process for new drugs: a cohort study. *BMJ Open* 2015;5:e006816.

The WHO ATC database was used to determine first-in-class status on the mistaken information that a first in class drug ended in a 01 number. After the paper was published the author was informed that this assumption was incorrect. Therefore, information from the United States Food and Drug Administration (contained in the new reference 10) was used instead to determine which drugs were first-in-class. The results from this reanalysis are quite similar and do not change the conclusions in the article.

Abstract – Data sources
Original: "World Health Organization Collaborating Centre for Drug Statistics Methodology"
New text: "United States Food and Drug Administration analysis of first in class new drugs"

Methods – Data analyses 5th paragraph
Original: "determined using the Anatomical Therapeutic Chemical (ATC) classification system from the World Health Organization {WHO Collaborating Centre for Drug Statistics Methodology, 2005 #18}. The 4th level ATC group for each drug was determined by searching the web site of the World Health Organization's Collaborating Centre for Drug Statistics Methodology. The 4th level is the chemical subgroup that the product belongs to. Drugs in the 4th level are listed in the order in which they appeared on the market and thus the first drug will have the numeral "01" at the end of its coding (10)."
New text: "based on an analysis of 645 new drugs approved by the United States Food and Drug Administration from 1987 to 2011.[10]"

Results – 4th paragraph
Original: "There were 33 drugs that were first in class. Comparing Health Canada's rating to the evaluations by the PMPRB/Prescrire, the negative predictive value was 89.5% (95% CI 66.8, 98.4) and the positive predictive value was 57.1% (95% CI 28.9, 82.2)"
New text (changes in bold): "There were **98** drugs that were first in class. Comparing Health Canada's rating to the evaluations by the PMPRB/Prescrire, the negative predictive value was **91.2**% (95% CI **80.7**, **97.1**) and the positive predictive value was **46.3**% (95% CI **30.7**, **62.6**)"

Discussion – 2nd paragraph
Original: "After drugs that were second or later entries into a class were removed, there was still a large difference between Health Canada's negative predictive value (89.5%) and its positive predictive value (57.1%)."
New text (changes in bold): "After drugs that were second or later entries into a class were removed, there was still a large difference between Health Canada's negative predictive value (**91.2**%) and its positive predictive value (**46.3**%)."

Table 4
Original: The numbers in the table reading from left to right currently are:
1st row 8 6
2nd row 2 17
New numbers:
1st row 19 22
2nd row 5 52

References – number 10

Original: "WHO Collaborating Centre for Drug Statistics Methodology. About the ATC/DDD system Oslo: Norwegian Institute of Public Health; 2005 [updated January 14; cited 2005 June 30]. Available from: http://www.whocc.no/atcddd/."

New text: "Lanthier M, Miller K, Nardinelli C, Woodcock J. An improved approach to measuring drug innovation finds steady rates of first-in-class pharmaceuticals. *Health Affairs* 2013;32:1433-9."

Below the table the positive and negative predictive values currently are:
Positive predictive value=57.1% (95% CI 28.9, 82.2)
Negative predictive value=89.5% (95% CI 66.8, 98.4)

They should be:
Positive predictive value=46.3% (95% CI 30.7, 62.6)
Negative predictive value=91.2% (95% CI 80.7, 97.1)

BMJ Open 2015;**5**:e006816corr1. doi:10.1136/bmjopen-2014-006816corr1