Article details: 2018-0146	
Title	**Cost recovery by Health Canada and drug safety: a time series analysis**
Authors	Joel Lexchin MSc MD
Reviewer 1	**Reviewer name withheld** **Reviewer comments are linked to original submission – see appendix for original submission**
Institution	Geriatric Medicine
General comments	Comments to the Author This manuscript describes an analysis of the number and type of safety warnings and market withdrawals of drugs before and after the implementation of 'cost recovery' fees collected by Health Canada. The following are questions and suggestions to improve the clarity of the paper: 1. what is meant by the statement "Health Canada could not guarantee that the criteria for including drugs in the list of NAS..." line 3, page 9? Can the author provide an illustrative example? 2. add "Canadian dollars" to paragraph describing funding of drug program (this should be obvious, since the text refers to Health Canada, but one never knows...) 3. [In the discussion section, to further illustrate the non-effects of the implementation of Health Canada 'user fees', listing the examples of the withdrawal of: rofecoxib, desfenfluramine, (post-cohort) and pergolide (pre-cohort), which older clinicians may recall were accompanied by stories in the popular press would link this study to a remembered outcome.] I place this suggestion in parentheses since identifying a particular drug in the text, rather than just keeping it listed in the details within the supplementary files may induce a reaction from the pharmaceutical industry. I defer to the wisdom and experience of the editors on this point. **[The author has considered these comments]**
Reviewer 2	REVIEW WITHHELD
Institution	
General comments	
Reviewer 3	**Reviewer name withheld** **Reviewer comments are linked to original submission – see appendix for original submission**
Institution	Health Services
General comments	Comments to the Author Cost recovery by drug regulators has been a controversial subject in many countries, including Canada. In this manuscript, the author conducts a pre-post study of safety outcomes approved by Health Canada before and after the advent of fee collection. While an important question, I have some concerns about the methodology. Major points 1) The methods of data collection appear sound, but the lack of guarantee from Health Canada is concerning. Do the data match what can be found about approval in the Drug Product Database? 2) The nature of the study means that any changes in the characteristics of drugs between the two periods could bias the results. Were they meant to treat the same conditions overall? 3) A survival analysis controlling for characteristics of the drugs (indication, utilization, etc.) would provide a more rigorous analysis method. 4) This treats Canada in a void – perhaps drugs coming to market sooner in the post period led to the lack of discovery of safety in the post period. This might have been faster as drugs may have been more likely to gain approval elsewhere in the world and begin accruing real world use. If this were the case, then this would mean that the drugs introduced in the post-period had shorter time to safety warning than those in the pre-period. Given the very substantial difference in median approval time, I believe this is a serious concern. 5) Given the methods, the conclusion is too strong. Further, if the author is going to suggest that “other consequences” be investigated, there should be some discussion of what those would be.

	Otherwise, the findings as they stand support the continued use of user fees, do they not? **[The author has considered these comments]**