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Title	Pediatric drug data in Canadian drug monographs: a descriptive analysis
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Reviewer 1	Michael Rieder
Institution	Department of Clinical Pharmacology, Children's Hospital of Western Ontario, London, Ont.
General comments (author response in bold)	The authors describe their work evaluating paediatric information in new drug approvals by Health Canada from 2007 to 2016 and found that the majority of drugs lacked paediatric specific indications. This is in contrast to developments in other jurisdictions and points to Canada as a stand-out from other major nations, and not in a good way. As a minor point did the authors consider removing from the denominator drugs for which there would never be a paediatric indication (for example, a drug for Lewy Body Dementia, which does not occur in children)? This may not impact much on the numbers but would be something to consider **Thank you for this comment. We have now reviewed all the drugs individually in regard to their indications and have excluded those which were indicated for adult specific conditions (n=5). This change has been added to our method and our result section has been fully updated. Please see our response to comment 1. (Our methods and results section now include an exclusion of drugs deemed irrelevant to pediatrics based on therapeutic indications for non-oncology drugs and based on molecular targets for oncology drugs. Tables 1-2, Figures 1-2, and Supplements 1-2 have all been updated after exclusion of drugs deemed irrelevant to pediatrics.)** As a methods point did the four reviewers ever disagree? It seems that in this case the senior reviewer would determine this - how often did this happen? **We have now added a section to our method and result section on the discrepancy of the results. Please see our response to comment 16. (Methods, Page 6, Line 16-18. Results, Page 7, Line 16-17.)** In the discussion on page 10 (line 47) the authors note "large pharmaceutical companies" - I think this statement applies to small and mid-size companies too. **We have changed "large pharmaceutical companies" to "pharmaceutical companies". (Interpretation, Page 12, Line 5.)** In the Conclusions I would combine the last two sentences together. **We have now combined the last two sentences of the conclusion and it reads as:** **"Such regulations will promote neonatal and pediatric drug studies and enhance the inclusion of existing pediatric information in Canadian drug monographs, all of which will contribute to optimal neonatal and pediatric pharmacotherapy in Canadian children." (Conclusion, Page 14, Lines 14-16.)**
Reviewer 2	Joel Lexchin
Institution	School of Health Policy and Management, York University, Toronto, Ont.

General comments (author response in bold)	This study looks at the availability of pediatric indications and information for new active substances approved in Canada from 2007-2016 inclusive. Since the authors are contrasting the situation in Canada with that in the United States and the European Union, they should provide some quantitative information about what percent of drugs have pediatric indications and information in these jurisdictions. If the authors don't have information about the US or the EU then there is no basis for saying that Canada is better or worse. I'm not totally convinced by the comparison of Canada to the US at the bottom of page 9. It was almost 20 years since the US passed the first pediatric regulatory initiative versus 10 years for Canada. Do the authors have information about the 2007-2016 period for the US? **We agree with the reviewers' comment and have changed the wording on this paragraph so that it will not reflect any direct comparison. Please see above, our response to comment 2.** The authors need to distinguish between the generation of pediatric data through Canadian trials and the provision of pediatric data to Health Canada that is available elsewhere. The two scenarios have different implications for moving forward. **We thank the reviewer for this important comment. We agree that reinforcement of Canadian trials for optimized generation of pediatric data and provision of pediatric data to Health Canada that is available elsewhere are two different avenues for optimizing the availability of pediatric data in drug labeling. Both strategies are needed in order to enhance the "availability" of pediatric data in drug labeling and subsequently decrease the off-label use of drugs in pediatric patients. In this current study, we aimed to provide original data and highlight the lack of pediatric information in the labeling of drugs approved by Health Canada and name a few of the avenues which might be of help with this important issue. We did not aim to provide strategic approaches for enhancement of either of the above avenues. (No corresponding changes in manuscript.)** Does the US and EU legislation mandate the development of pediatric-friendly oral dosage forms or just information about pediatric use. If it's only information about pediatric use, then I'm not sure why the authors collected data about pediatric-friendly oral dosage forms in Canada. **Child-friendly, age-appropriate drug formulation is an essential part of pediatric pharmacotherapy. In this project, we aimed to investigate the quantity and quality of pediatric information in Health Canada new drug approvals without any direct comparison with US or European drug approvals. Furthermore, under Pediatric Research Equity Act (2003), any pharmaceutical company seeking approval for a drug with possible benefits in patients <6 years of age, should make reasonable attempts to produce a child-friendly, age-appropriate drug formulation. (No corresponding changes in manuscript.)** The authors are rightly concerned about how the lack of pediatric indications and information affects pharmacotherapy for children but do they have any quantitative data about this problem? **Lack of pediatric indications and information result in off-label use of drugs**

	in pediatrics. A literature review of unlicensed and off-label drug uses revealed that use of off-label medication in pediatric inpatients could be up to 66%. Inadequate understanding of appropriate dosage, safety, or efficacy is known to be associated with risk of therapeutic failures, adverse events (relative risk 3.44) and medication errors (50%) (Neuspiel and Taylor, 2013; Conroy 2010). (Introduction, Page 4 Line 16. **"These regulatory initiatives have resulted in pediatric drug trials, with subsequent labeling changes to include important safety and efficacy pediatric data and decrease the use of off-label drugs with known risk of therapeutic failure and adverse events[7,8]."**) Page 4, line 45: What do the authors mean by "global leaders"? **We have now changed the word "global leaders" to "jurisdictions like the United States, Europe and Japan." (Introduction, Page 4, Lines 18-20.)** Page 4, line 54: The authors should explain what they mean by data protection. **We have now changed the phrase "eight-year period of data protection" to "eight-year period of market exclusivity". (Introduction, Page 5, Line 1)** Page 5, lines 22-24: The authors should provide information about how the performance reports were accessed since they are not posted on a publicly available website. **We have added the following information to the method section of our manuscript: We identified new active substances (NASs) approved by Health Canada between January 1, 2007 and December 31, 2016 using the Annual Drug Submission Performance reports (accessed upon e-mail request from Health Canada). (Methods, Page 5, Lines 11-14.)** Page 6, line 3: What ATC level did the authors use? **Please see our response above to comment 4.** Page 9, line 15: How do the authors know whether or not pediatric information was available in other jurisdictions? **We have changed this sentence from "submit to Health Canada existing pediatric information available in other jurisdictions" to "submit existing pediatric information to Health Canada" to refer to the available pediatric information in general. (Interpretation, Page 10, Lines 10-13.)** Page 9, line 28: When the authors refer to the "market-exclusivity regulation" are they referring to the Pediatric Extension? **We have changed the phrase "implementation of Health Canada's market-exclusivity regulation" to "implementation of Health Canada's Pediatric Extension legislation." (Interpretation, Page 10, Lines 17-19.)** Page 11, lines 3-8: The Canadian regulatory environment is no more or less complex than the ones in the US or the EU. There is a gap between when a drug is approved for marketing and when it might be listed on a provincial formulary but that has nothing to do with whether or not pediatric information is available on the drug. **Thank you for this comment. We have now changed this paragraph to read**

	as follows: **"This delay in the new drug submission is primarily due to Canada being a small market. Authorizing Health Canada, to proactively mandate the submission of pediatric data from manufacturers combined with appropriate incentives would be a significant step to rectifying this situation." (Interpretation, Page 12, Lines 7-9.)** Page 11, lines 17-19: What do the authors mean by "appropriate incentives"? **We have taken the word "appropriate" out of this sentence to read as: "Authorizing Health Canada, to proactively mandate the submission of pediatric data from manufacturers combined with incentives would be a significant step to rectifying this situation." (Interpretation, Page 12, Lines 9-11.)** Page 11, line 28: Drug shortages are mainly for generics. What is the relevance of drug shortages to the provision of pediatric information? **We have now taken the comment on drug shortage out of this section of the manuscript** Page 12, line 8: The authors need to provide a reference for their statement that the pediatric regulatory environment in the EU and US has resulted in a global collaboration. **We have now added a reference for this statement (Thomsen, 2019) (Interpretation, Page 13, Line 5.)** Page 12, line 10: The authors need to provide a reference for the statement that there has been a clear advance in pediatric drug development over the past 20 years. **We have now added a reference for this statement (Bucci-Rechtweg, 2017). (Interpretation, Page 13, Line 7.)** Page 12, line 54: The authors could have gotten a summary of the pediatric information available when a drug was first introduced by looking at the edition of the CPS when the drug was initially marketed as the monographs in the CPS are summaries of the official PM. **We thank the reviewer for this comment. We designed the current project with aim to review the "current" availability of pediatric information in Health Canada new drug approvals over a recent 10 year period. Our data reflect the information that is currently available to patients and healthcare practitioners. In our future study, where we aim to compare the availability of pediatric information in new drug approvals by Health Canada vs FDA, we will review all the original labeling along with the most updated ones. (No corresponding changes in manuscript.)**