Article details: 2020-0036	
Title	Factors associated with drug shortages in Canada: a retrospective cohort study
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Reviewer 1	Joel Lexchin
Institution	School of Health Policy and Management, York University, Toronto, Ont.
General comments (author response in bold)	This study looks at the reasons for drug market shortages in Canada. 1. Page 5, lines 45-49: Are the reasons for shortages the same in different markets? **We have presented the underlying causes identified by previous empirical studies in terms of the country (the US) and drugs (last paragraph, page 4).** 2. Page 6, lines 17-22: What is the evidence that manufacturers are complying with mandatory reporting? **The report by Donelle et al. (2018) showed an apparent surge in drug shortage reporting since March 2017 compared with the previous voluntary period. In addition, according to Health Canada (personal communication), "Timely public communication of drug shortages and discontinuations by drug companies is an essential part of preventing and managing shortages. It helps the drug supply chain and the healthcare system respond appropriately in order to minimize the impact on patients. It is Health Canada's expectation that companies report accurate and timely information in accordance with the regulatory requirements set out under the Food and Drug Regulations. When Health Canada is made aware of a drug shortage or discontinuation that is not reported in accordance with regulatory requirements, the Department takes action to ensure that the company is reporting shortages according to the regulatory requirements." We have provided the evidence in Appendix 1.** 3. Page 7, line 22: Although the authors give a reference to consult for definitions they should define the term "ethical" in the text. **As suggested, we have defined the term "ethical" products as those that do not require a prescription but are generally prescribed by medical practitioner for unscheduled professional use (e.g., hemodialysis solution) and emergency use (e.g., nitroglycerine) (Appendix 1).** 4. Page 7, lines 36-40: Combining DINs with these characteristics into a single market seems to assume that they are interchangeable but that may not be the case. For example, a 10 mg capsule cannot be cut in half to substitute for a 5 mg capsule that is in short supply. **Thank you for your comment on this. You were correct that a 10 mg capsule cannot be cut in half to substitute for a 5 mg capsule that is in short supply although the reverse substitute is feasible. In this revised manuscript, we have re-defined our "market" as a group of DINs with the same active ingredients, dosage form, route of administration and strength in our main analyses (2nd and 3rd paragraph, page 6). In the sensitivity analysis, we defined the "markets" as DINs with the same active ingredients, dosage form, and route of administration (last paragraph, page 7).** 5. Page 9, line 3: What statistical software was used? **SAS was used (last paragraph, page 7).** 6. Page 9, line 31: How are the authors defining the term "complex"?

	We have defined the complexity level by the dosage form and route of administration from a manufacturing viewpoint (1st paragraph, page 7) according to Danzon and Furukawa (2011) and the report of Multi-Stakeholder Steering Committee on Drug Shortages (https://www.drugshortagescanada.ca/files/MSSC_Causes_and_Prevention_2017.pdf). 7. Page 10, lines 42-47: The authors need to clarify the difference between "compliance issue with the manufacturing process" and "disruption in the manufacture". **We have mentioned that the reasons were provided at the website as exclusive options for manufacturers to choose to report. However, these reasons could be overlapping and manufacturers may choose what they like to report (may or may not reflect a truthful report). We have acknowledged the limitation in the "Interpretation" section (1st paragraph, page 14).** 8. Page 11, line 31: Although later in the manuscript the authors comment briefly about how provinces control the price of generic drugs I feel that they need to provide a somewhat more detailed description. **As suggested, we have provided more detailed description about how provinces control the price of generic drugs (page 13).** 9. Page 11, line 31: Does "complicated" mean the same thing as "complex"? **We have used a consistent term, "complex", in the manuscript.**
Reviewer 2	Gregory Kline
Institution	Medicine/Endocrinology, Cumming School of Medicine, University of Calgary, Calgary, Alta.
General comments (author response in bold)	In this manuscript, the authors investigate one of the most pressing problems in Canadian health care – drug shortages. This increasingly frequent problem is, at best, greatly frustrating to patients and physicians and, at worst, potentially life-threatening. A better understanding of the underlying factors behind drug shortages is greatly needed in order to inform health policy at government levels. This reviewer is definitely in favour of seeing a careful analysis of the factors behind drug shortages as it is probably the only way this problem can be addressed at a health care systems level. Although the present manuscript is a step in the right direction, there are two major flaws that limit its validity: 1. The list of potentially explanatory factors behind market shortages is far too narrow and seems to completely ignore trends related to costs, reimbursement and need. **In this revised manuscript, we have also analyzed drug shortages at the DIN level. We considered the listing on provincial formularies as a factor when conducting the analysis among all DINs and the drug listing price as a factor when conducting the analysis among DINs listed on formularies. At the market level, we have also added the proportion of DINs on formularies as a potential factor.** 2. The analysis is heavily dependent upon market history and product factors and even those cannot be assumed to be comprehensive in explaining what is actually happening in pharmaceutical manufacturing firms. The most telling suggestion of this is seen in Appendix Table 2 where "business/economic reasons for shortages" is only ever admitted in 1% of all shortages. This seems to indicate that the database used for this analysis is, at best, a very superficial overview of what *might* be happening behind the scenes in the Canadian pharmaceutical industry. **The website provides main options of shortage reasons (shortage of an active ingredient, shortage of an inactive ingredient or component, disruption of the**

	manufacture of the drug, requirements related to complying with good manufacturing practices, delay in shipping of the drug, and demand increase for the drug) for manufacturers to choose, which did not include business/economic reason as one option. However, manufacturers could select the "other" option and then comment that the shortage was related to business. We agree that the reasons might not well reflect what is actually happening. We have acknowledged this limitation in our "Interpretation" section (1st paragraph, page 14). 3. In addition, there are many missing statistical calculations and descriptions throughout the data analysis. **We have added detailed statistical calculations and descriptions for our data analysis (2nd paragraph on page 7).** Abstract: 4. I am confused by the use of the term "ethical drug" – this is not common parlance in medicine and the dictionary defines this as any drug requiring a prescription. Thus I am confused when the authors say the analysis excluded ethical drugs – I think the authors mean that they restricted the analysis to ethical drugs? (question also applies to similar wording in methods) **We have defined the term "ethical" products as those that do not require a prescription but are generally prescribed by medical practitioner for unscheduled professional use (e.g., hemodialysis solution) and emergency use (e.g., nitroglycerine) (Appendix 1).** Methods 5. Note that PharmaClick should be Pharmaclik **It has been corrected.** 6. Please provide a bit more information on Pharmaclik. The website requires some type of membership and so is not available for inspection. Where does the information on the site come from? Why did the authors choose to use this as a data source and exactly what kind of data did they abstract from this site? **We have provided more explanations what kind of data we abstracted from this site (Appendix 1). Please see our response to the same comment 5c from the meeting of the Scientific Editors above.** 7. The sentence "our main outcome is the indicator of a drug shortage at the market level" seems vague – I don't understand exactly what this means. What is "the indicator of a drug shortage" and how is that an outcome? **We have changed the sentence as "Our focus was on shortages at the market level, which occur when all manufacturers of the same interchangeable drug report shortages" (3rd paragraph, page 6).** 8. Please clarify "market age" (I'm guessing this is the duration of time since the drug compound came to market – but most CMAJ readers will not have an economics background so we need more explanation). Plus, does this include both on-patent and off-patent time? Or just that which is relevant to the branded vs generic manufacturer? **We have defined the "DIN age" at the start of follow up as the duration of time since the DIN came to market for our analysis at the DIN level (Appendix 1). Also, we have excluded market age as a factor in our analysis at the market level due to a wide**

	variability of market age for branded DINs and generic DINs (often a 12-20 year lag after the patent of the Branded DINs expires) under the same market. The market structure has indicated the levels of the market age if using market age of the branded DINs as the age of the markets. 9. If market age is defined as above, why did the authors perform this analysis as a dichotomous < 5 yrs vs > 5 years analysis? What is special about 5 years? Wouldn't it be preferable to perform an analysis that sees market age as a continuous variable? **As mentioned above, we have excluded market age as a factor in our analysis at the market level. In terms of the market age at DIN level, it is now modelled as a continuous variable for branded DINs. We have described how we determined using a continuous age variable for branded DINs and how we chose the cut-off values to dichotomize at 3 years for generic DINs in Appendix Table 3.** 10. I am surprised that the authors did not consider more factors as potentially associated with drug shortages – especially: drug cost, proportion of provinces where the drug is listed on provincial reimbursement formularies and especially drug utilization data (i.e. frequency of use). These might all be very important predictors – one might suspect that low cost drugs with low utilization rates might be highly prone to shortages as might non-reimbursed drugs with low utilization rates? **We have added the number of provincial formularies the DIN was listed on as a factor when conducting the analysis at the DIN level among all drugs and listing drug price as a factor when conducting the analysis among drugs listed on formularies. At the market level, we have considered the proportion of DINs on formularies as a factor. We found that markets with a higher proportion of DINs on formularies (Table 2) and generic DINs with more provincial formulary coverages (Table 3) were more likely to be in shortage. Unfortunately, we could not access the drug utilization data for all drugs and we have acknowledged this as one limitation in the "Interpretation" section (1st paragraph, page 14).** 11. In the interpretation section, the authors say that prices were not considered relevant as their study focused on market level and not specific drug versions. They also claim that drug pricing in Canada is complex (and they elaborate almost too much upon this) and thus beyond the scope of the study. I am not convinced by their explanations and I disagree that comparing prices across different types of drug markets is not meaningful – indeed, it is very meaningful! We need to know if drugs that cost $20 per month are more likely to go into shortage vs drugs that cost $300 per month, as a general principle and irrespective of the therapeutic class. It does not seem unreasonable to ask the authors to categorize the drugs into just 4 or 5 broad cost groups – such an analysis could permit some degree of cost variation between similar classes, provinces and suppliers to be accounted for, without hiding any trends that are present. **We have added the listing drug price as a factor when conducting the analysis at the DIN level among drugs listed on formularies (Appendix Table 8).** 12. Although it is beyond the ability of the authors to control, it must be recognized that the Canadian Drug Shortage Database relies upon manufacturer reporting; stated reasons are simply those that the manufacturer wishes to report – which may or may not reflect a truthful report. "Disruption of the manufacture of the drug" is an example of a catch-all phrase that might represent many underlying problems with the manufacturer or could be used to hide a deliberate economics-based decision by the manufacturer. This should be acknowledged as a limitation.

	We agree with the reporting problems regarding the stated reasons and have acknowledged it as a limitation as suggested (1st paragraph, page 14). 13. It would be standard to report the statistical software used in the analysis. **We have reported the software we used, which is SAS (2nd paragraph, page 7).** Results 14. The authors report higher shortages in markets that were "more complex with respect to route/form." In the methods section, the authors indicate a planned analysis by route/form but they do not describe what constitutes "more complex route/form" – please clarify. **We have defined the complexity level by the dosage form and route of administration from a manufacturing viewpoint (1st paragraph, page 7) according to Danzon and Furukawa (2011) and the report of Multi-Stakeholder Steering Committee on Drug Shortages (https://www.drugshortagescanada.ca/files/MSSC_Causes_and_Prevention_2017.pdf).** 15. Page 9, lines 33 to 40 seem to report the frequency of shortages among three types of drug administration routes. However, there is no statistical analysis performed to demonstrate if these are significant differences (and probably need to mention this in the stats methods too). **Those sentences have been deleted. Instead, we have now stated that "other complex route/form" and "oral non-solid" had a higher probability of being in shortage (1st paragraph, page 8). Using a logistic regression model, we have tested the differences (Table 2).** 16. The group "drugs for sensory organs" needs clarification. I gather this is an ATC classification but examples would be helpful as most physicians would not be familiar with the classification system. **Examples have been provided for each ATC classification in Appendix Table 2.** 17. When the authors state that drugs for sensory organs were most likely to be in shortage – there is no comparison stated and apparently no statistical testing done. **We have stated that they have a higher probability of being in shortage (1st paragraph, page 8). Using a logistic regression model, we have tested the differences (Table 2).** 18. Appendix table 2 is discussed in the text but no actual data or statistical analysis is presented; if it is important then some actual data should be presented. If unimportant than the discussion may be deleted. **As suggested, we have deleted the relevant discussion.** Interpretation 19. The authors make an unwarranted leap when saying that single generic manufacturers' related drug shortages were due to low profit margins. At best this is pure speculation but without any cost data presented, it cannot be accepted. Perhaps it is due to low reimbursement rates in provincial formularies? Perhaps it is due to very low utilization rates? Perhaps it is due to the presence of many therapeutically-related options (i.e. consider the multitude of anti-hypertensive classes). Admittedly all these alternative explanations could factor into overall profits but not necessarily profit margins. Without

	further explanation or data to support it, the authors miss the opportunity to expound upon the factors, both manufacturer-specific and health system-specific that impact the incentive to maintain drug supply. **As suggested, we have provided more analyses to support our interpretation. At the DIN level, we have included provincial formulary listing (or listing price in the subgroup analysis), therapeutically related options (ATC classification) and manufacturer characteristics in the analyses. At the market level, we have included reimbursement rates in provincial formularies (i.e., the proportion of DINs listed on formularies) and ATC classification in our analyses.** 20. After a discussion of not-for-profit pharmaceutical manufacturing as a solution to drug shortages, the authors make a very surprising statement on page 13, line 45 " we are not advocating the formation of such a state-owned enterprise." This seems entirely contradictory to where this whole study is pointing and seems to belie some political convictions on the part of the authors? Unless it is better explained, this is wholly inappropriate for a scientific paper. **We have removed that sentence and agree that a not-for-profit generic pharmaceutical manufacturer as a supplement to instead of a replacement of all the existing generic manufacturers might help address the shortages. However, this depends on whether Canadian governments were to explore this option. The changes were made in the 1st paragraph on page 15.** 21. It seems surprising that markets with fewer suppliers were more vulnerable to shortages, especially for off-patent drugs. Other data would suggest that markets with many suppliers would be more vulnerable to shortages due to a progressively smaller piece of the pie available in an off-patent market. Perhaps this should also be discussed (as it is also a good argument for a single, government-run manufacturer). **To clarify, the drug shortage at the market level implies that all DINs under the market were in shortage. Our analysis results at the market level suggest that markets with a single generic supplier were the most vulnerable to shortage (last paragraph, page 10). Markets with multiple generic manufacturers were less likely to be in shortage than all other markets. At the DIN level, we found that branded DINs or generic DINs in the markets with branded manufacturers and a single generic manufacturer were the most likely to be in shortage (last paragraph, page 11). As suggested, we have discussed that "As suggested by our study findings, a not-for-profit generic pharmaceutical manufacturer as a supplement to instead of a replacement of all the existing generic manufacturers might help address the shortages." (1st paragraph, page 15).** 22. It is inappropriate to present new data in the interpretation section (i.e. mention of the exploratory analysis of <2 year market age) – this should all be presented in the results section if it is relevant. **As suggested, we have removed this from the interpretation section and presented the results at different cut-off values for DIN's market age in Appendix Table 3.** 23. Table 3 is not clear – please explain the statistical testing involved in generating these numbers. **We have added a note to explain that the results were based on a truncated negative binomial regression (now in Table 4).**
Reviewer	Brian White-Guay

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Institution	Faculté de Pharmacie, Université de Montréal, Montréal, Que.
General comments (author response in bold)	General comments: 1. This manuscript addresses a very relevant topic and the main objective was to analyze drug shortages for drug products marketed in Canada for a period of 18 months from March 14, 2017 to September 12, 2018. The authors also report on additional analyses of factors associated with shortages taking into account (1) market structure (2) market age and (3) route/dosage form. **The main shortcoming of this manuscript is in the choice to focus only on a high level indicator of drug shortage at the market level where a market is defined to be in shortage if all dosage strengths in a market and all of their package sizes are reported to be in shortage. This implies a fairly restrictive and active pharmaceutical ingredient (API) specific inclusion requirement to meet a shortage definition. Though this approach offers an interesting period estimate of an 'absolute' API specific market shortage it fails to provide a sufficiently detailed analysis of the study sample data set that would allow readers to better appreciate the clinical relevance and possible impact of the frequency of shortages of various dosage strengths and generic/branded products within a market and how such risks might be mitigated by an alternate acceptable pharmaceutical class substitution (ex. Recent sartan (ARBs) tainted manufacturing supplies).** **In the revised manuscript, we have conducted the analyses at the market level and the DIN level. We re-defined our "market" as a group of all DINs with the same active ingredients, dosage form, route of administration and strength (2nd paragraph, page 6).** 2. Another important limitation to the interpretation of the results is the implicit assumption that drug products obtaining a drug identification number (DIN) from Health Canada are available in 'uniform markets' across the country. In reality each publicly funded drug plan across provinces and territories provides coverage to its eligible population based on a unique plan design, list of approved drugs (formulary) and reimbursed costs, hence the data as presented cannot be interpreted in this regard (1). **We agree that the DINs could be covered by the publicly funded drug programs of different provinces and territories in Canada. At the DIN level, we have considered the number of provincial formularies the DIN was listed on as a factor when conducting the analysis among all DINs and the drug listing price as a factor when conducting the analysis among DINs listed on formularies. At the market level, we have also added the proportion of DINs on formularies as a potential factor.** 3. Last but not least, there is no relevant discussion of the study limitations. **We have discussed study limitations in the "Interpretation" section (last paragraph on page 12 to 1st paragraph on page 14).** Specific comments : Introduction : 4. This section reads somewhat like a hybrid of an introduction and a conclusion. It should focus more on the specific topic of the challenges and limitations of the study of drug shortages in Canada and it should be revised accordingly to focus on the research conducted. **As suggested, we have made changes to focus on the research conducted in the**

	"Introduction" section (pages 4 and 5). Methods: This section requires several additional points of clarification: Study data and sample 5. -The authors included both existing shortages and new ones over the study period. Presumably there were existing shortages on March 14 2017 (start of mandatory reporting) and this should be included in the analysis as on-going shortages rather than new ones. **Drug shortage database starting from March 14, 2017 (mandatory reporting) to September 12, 2018 (about 18 months) was extracted from the Canadian Drug Shortage website. All ongoing shortages as of March 14, 2017 and all new shortages that occurred during the study period were included in the study (2nd paragraph, page 5). In our analysis, the outcomes (the binary outcome and duration) were defined the same way for both types of shortages and we did not distinguish them.** 6. -The authors do not provide any information or comment on discontinuations which are sources of shortages in single branded or generic source markets **According to the drug shortage website and Health Canada, a shortage is a situation in which a manufacturer is unable to meet demand for a drug that has been approved in Canada. A discontinuation is a situation in which a manufacturer permanently stop selling a drug, which is different from shortage. To keep the definition of drug shortage in our manuscript consistent with the definition used by the reporting website and Health Canada, we focused on the reported shortages in our analysis. We agree that discontinuations could be the sources of shortages. According to the "Guide to reporting drug shortages and discontinuations" (https://www.drugshortagescanada.ca/blog/11), when a drug is in shortage and manufacturers decide to discontinue its sale, they must report drug shortage to indicate that they no longer intend to meet demand and report the reason for the shortage to indicate that the shortage is due to the drug discontinuation. Some of the reported drug shortages were due to the discontinuation which was categorized as "business/economic reason" (Appendix 2). Thus, our analyses have captured drug shortages due to discontinuation.** 7. -There is no information provided by the authors on steps taken to validate the integrity and completeness of the Canadian Drug Shortage Database (CDSD).What is the level of compliance by manufacturers? **The report by Donelle et al. (2018) showed an apparent surge in drug shortage reporting since March 2017 compared with the previous voluntary period. In addition, according to Health Canada (personal communication), "Timely public communication of drug shortages and discontinuations by drug companies is an essential part of preventing and managing shortages. It helps the drug supply chain and the healthcare system respond appropriately in order to minimize the impact on patients. It is Health Canada's expectation that companies report accurate and timely information in accordance with the regulatory requirements set out under the Food and Drug Regulations. When Health Canada is made aware of a drug shortage or discontinuation that is not reported in accordance with regulatory requirements, the Department takes action to ensure that the company is reporting shortages according to the regulatory requirements." We have provided the information in Appendix 1.** 8. -There is a mention on Line 10-11 of other sources used in addition to the drug shortage

database (DPD,PharmaClick) but the text does not specify what these sources were used for in the study.
As suggested, we have specified what each of these data sources were used for (Appendix 1, Appendix 2 and Appendix Table 1).

9. -Line 38 states that DINs with same active ingredients, dosage form and route of administration were organized into a group called a "Market". Why is dose strength not specified as well?
As suggested, we have changed our definition into "DINs with same active ingredients, dosage form, route of administration and strength were organized into a group called a "Market"" (2nd paragraph on page 6).

Main outcome and factors
10. -The authors do not provide a rationale or references for the choice of the indicator selected for shortage at the market level.
Based on the previous similar studies and our available data, we considered the potential factors in our analyses (last paragraph, page 6). In the revised manuscript, we have also provided information on how we selected the factors included in our final models ("What factors were included in final regression models was determined by their univariate analysis results ($p<0.2$) and the Akaike information criteria." 2nd paragraph, page 7).

11. -There is no rationale for the selection of 5 years as the cut-off point to analyze market age and it should be justified
As mentioned above, we have excluded market age as a factor in our analysis at the market level. In terms of the market age at DIN level, it is now modelled as a continuous variable for branded DINs. We have described how we determined using a continuous age variable for branded DINs and how we chose the cut-off values to dichotomize at 3 years for generic DINs in Appendix Table 3.

12. -The authors have chosen quite appropriately to use the ATC classification but the choice of using only Level 1 is unfortunate as the relevance of the analysis would have been enhanced for the journal audience by using at least Level 2 and even furthermore with Level 3.
We have reported the drug shortages by ATC level 3 in Appendix Table 2. However, there was not enough sample size for us to include the level 2 or 3 in our regression analysis.

13. -The authors have summarized the reasons reported for drugs in shortage and the data is presented in Appendix Table 2.They explain that they created additional reasons to the ones offered by the CDSD .It is unclear however how many of these reasons would be mutually exclusive for classification purposes (ex. Demand increase for the drug; Insufficient supply; Shortgage of an active /inactive ingredient or component could all overlap with 'demand increase for the drug').
We have mentioned that the reasons were provided at the website as exclusive options for manufacturers to choose to report (Appendix 2). However, these reasons could be overlapping and manufacturers may choose what they like to report (may or may not reflect a truthful report). We have acknowledged the limitation in the "Interpretation" section (1st paragraph, page 14).

Results:

	14. -Line 22 states that the analysis included 2023 markets including 10067 DINs .This should be referenced to Table 1 and 2023 should appear in Total N. **As suggested, the N has been added to Table 1.** 15. -Line 22-23 indicate that 12.2% of markets were in shortage during the study period, an impressive figure given the definition of a market used by the authors but it is impossible to assess the possible clinical impact and the trend over time. **Our new analysis results showed that 13.3% of markets were in shortage during the study period and the shortage duration among markets being in shortage was 136.6 days (1st paragraph on page 8). We examined the number of DINs with shortages (ongoing vs. new) over time but did not find apparent trend. This could due to the short study time period (18 months). We are planning to assess this in our future research.** 16. -Line 31 refers to markets that are 'more complex' but there is no comment on the attributes used for this qualification. From a manufacturing viewpoint, injectable and non-injectable sterile products and modified release formulations are more complex but what are the criteria used here? **We have defined the complexity level by the dosage form and route of administration from a manufacturing viewpoint (1st paragraph, page 7) according to Danzon and Furukawa (2011) and the report of Multi-Stakeholder Steering Committee on Drug Shortages (https://www.drugshortagescanada.ca/files/MSSC_Causes_and_Prevention_2017.pdf).** 17. -The sensory organ ATC class was identified as the most likely to be in shortage but the impact might be quite less than other classes and this is not addressed in the results section. **Due to a lack of data, we could not comment or discuss the shortage from which ATC classification would have more impact. This really depends on whether they have safe and effective alternatives for the patients who use these drugs. It will be great to examine the impact of these shortages in the future.** Interpretation: 18. - Since markets with a single generic manufacturer tended to have a longer duration of shortage than markets with branded-manufacturers only, this would have been interesting to further discuss. The hypothesis of lower profit margins as an explanation should be supported since it does not appear always consistent with recent examples of pricing practices of single market generic suppliers in the US. **We have provided more background on the generic drug pricing policies in Canada (which is much different from those in the US) to support why lower profit margins was an explanation for the drug shortages (last paragraph on page 10 and on page 13).** 19. -In the US, a drug shortage generally means a period when the demand or projected demand for the drug within the United States exceeds the supply of the drug. In 2017, there were a total of 39 new drug and biological product shortages identified and 135 prevented by FDA. The authors should attempt to put their results in perspective since Canada's experience with shortages as defined by the authors appears substantially worse for no obvious reason.

	A shortage is a situation in which a manufacturer is unable to meet demand for a drug that has been approved in Canada. In our revised manuscript, we have defined a shortage at the DIN level as well as shortage at the market level. At the market level, 13.3% markets (n=462) were in shortage and among these 462 markets in shortage, the mean number of drug duration was 136.6 days. We have provided more background on the generic drug pricing policies in Canada (which is much different from those in the US) to partially explain a different experience with shortages in Canada (page 13). 20. - The suggestion that manufacturers pay more attention to the supply of the relatively newer products rather than older products is interesting but should also be supported. **It is well known that generic suppliers have a rapidly eroding market share opportunity depending on the order of entry into the market following the end of patent exclusivity and these trends tend to last except in special circumstances or supply decisions made by reimbursement bodies.** **As mentioned above, we have excluded market age as a factor in our analysis at the market level. In the revised manuscript, we have considered market age of DINs in our analysis at the DIN level. We found that relatively newer branded and generic DINs were less likely to be in shortage for a given market structure (e.g., markets with a single generic manufacturer). We agree that a rapidly eroding market share by the order of entry into the markets (the less share for the later entrants/relatively newer entrants) could be another possible explanation for our findings. We have added this information in the last paragraph on page 11.** 21. - The authors could have discussed how large multi-product firms dominate generic manufacturing and the impact this might have on supply ….given that in the US 80% of ANDAS are held by 7% of ANDAS sponsors (2). Based on various sources, the situation in Canada is close to the US one in this regard. **The situation in Canada is close to the US. As suggested, in the analysis at the DIN level, we have considered firm-level characteristics such as manufacturer size (number of DINs), top 50 manufacturer or not in terms of their sales in public insurance programs, and manufacturer type (mainly branded, mainly generic, and mixed). We have also reported drug shortage status for manufacturers with at least 5 DINs in shortage in Appendix Table 4.** 22. -The authors state that they considered all active drugs used both in the community and hospital settings as a study strength and we would agree but they should have provided the corresponding analysis of shortages by respective community and hospital setting. **Although we have considered all active drugs used in both the community and hospital settings, we could not distinguish the drugs solely used in hospitals from those in the community. However, we have conducted a subgroup analysis among drugs listed on provincial formularies (results shown in Appendix Table 8). These drugs are covered by publicly funded insurance programs and represent drugs mainly used in community setting (dispensed in community pharmacies) (2nd paragraph, page 12).** 23. -There is little or no discussion offered on study limitations and this should be addressed given the above. **We have discussed our study limitations (last paragraph on page 12 to 1st paragraph on page 14).**