Appendices (as supplied by the author)

Appendix 1. Details on the main data sources and study design

Data Sources

1. **Canadian Drug Shortage database** from the website, https://www.drugshortagescanada.ca: Many manufacturers have started voluntarily reporting drug shortages since 2012. On March 17, 2017, the reporting became mandatory. The mandatory reporting requirement had been notified by Health Canada at least one year before the actual effective date, March 17, 2017. According to Health Canada (personal communication), "Since March 2017, the *Food and Drug Regulations* (*Regulations*) have required drug companies to publicly report drug shortages and discontinuations, including the reasons for the shortage or discontinuation, within a specified timeframe on a third-party website (http://drugshortagescanada.ca/). According to the *Regulations*, drug companies must report drug shortages and discontinuations

- no less than six months in advance (if it is likely to begin in more than six months) or
- within five days of becoming aware of the drug shortage or discontinuation if it will begin within six months.

The *Regulations* also make it mandatory to update any posted information on the website within two days of becoming aware of the change. More specifically, according to the https://www.drugshortagescanada.ca/files/GUI%200120%20Drug%20Shortage%20Guidance_2017.pdf, the timeline requirements for reporting for the following situations are:

- You anticipate a shortage for your drug and you believe it will begin more than six months from today.
  - Post a shortage report at least six months before you anticipate the shortage will begin.
- You anticipate a shortage for your drug and you believe it will begin six months from today or less.
  - Post a shortage report within five calendar days from the day when you became aware that a shortage is likely to occur.
- You became aware that your drug is in shortage. You did not anticipate the shortage.
  - Post a shortage report within five calendar days from the day you became aware of the shortage.
- You became aware that your drug – for which you have already reported an anticipated shortage – is now in shortage.
  - Update the shortage report within two calendar days from the day you became aware that the shortage began, to indicate the date when the shortage started.
- The information you posted about a drug shortage changed.
  - Update your shortage report within two calendar days of becoming aware of the change.
- The shortage for your drug is resolved.
  - Update your shortage report within two calendar days from the day you can meet demand to include this date.

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. If Health

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Canada becomes aware that a drug company is not meeting its regulatory obligations for reporting drug shortages or discontinuations, it will take appropriate action in line with our Compliance and Enforcement Policy (POL-0001). Several compliance and enforcement options are available to address non-compliance and mitigate risks to Canadians, including compliance letters, on-site visits and public communications. The Department encourages anyone who becomes aware of a shortage that should be reported to provide this information to Health Canada by emailing: hc.drug.shortages-penurie.de.medicament.sc@canada.ca. Drug manufacturers input information to the third-party website. In instances when Health Canada becomes aware of errors in the data, it follows up directly with the company to ensure the accuracy of the information posted online." In addition, the report by Donelle et al.[1] (2018) showed an apparent surge in drug shortage reporting since March 2017 compared with the previous voluntary period.

The database contains information on the specific package size of a drug identification number (DIN) that was reported in shortage, the actual shortage start date, shortage reasons, estimated shortage end date, and actual shortage end date, if available, where DIN is a unique number to indicate a drug's active ingredients, strength, dosage form, route of administration and manufacturer while the package size distinguishes different package sizes for each DIN. Manufacturers can select one reason from the following options for their drug shortage cases: 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. Otherwise, there is an "Other (Please describe in comments)" option for manufacturers to choose and specify the reasons. We reviewed the comments provided but still found 3.4% of the reasons reported as missing or uninterpretable. It is not possible to know how accurate the manufacturers own reports of the reasons for the shortage are and thus we have acknowledged the limitation in the "Interpretation" section of the main manuscript. In addition, the website was designed with different date fields for shortage reports by the manufacturers. The estimated end date and actual end date were used to determine the status of the individual shortage report. For example, a report will have a shortage status of "Resolved" when an actual end date is entered and is in the past. A report will have a status "Actual shortage" indicating the shortage is still ongoing until an actual end date is entered.

The data fields [DIN, package size, actual shortage start date, 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, demand increase for the drug, or other), estimated shortage end date, and actual shortage end date, if available] for reported drug shortages from March 14, 2017 to September 12, 2018 were extracted from the website[2] by Daphne Guh. It was not conducted in duplicate and no agreement is required.

2. Health Canada's **Drug Product Database (DPD)**[3]**:** The DPD is maintained and updated nightly by Health Canada to report the information on drugs authorized for sale by Health Canada. This is a reliable data source that many other organizations in Canada is using, for example, a third party claims adjudicator, provincial formulary, insurance company, and the

Canadian Institute for Health Information (CIHI). The DPD contains detailed drug information on all drugs that are available in Canada, which includes DIN, drug name, each DIN's active ingredients, strength, dosage form, route of administration, manufacturer, package size, Active Ingredient Group number (a 10 digit number that identifies products that have the same active ingredient(s) and ingredient strength(s)), Anatomical Therapeutic Chemical (ATC) classification, schedule (prescription, Controlled Drugs and Substances Act (CDSA), Biological, over the counter (OTC), the "Ethical" products 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),[4] etc.), market status (marketed, cancelled, dormant) and status date.[4] These data fields were extracted from the last updated by Health Canada on April 12, 2019 on the Health Canada DPD data extract website.[3] It was not conducted in duplicate and no agreement is required.

3. **Formulary data** in nine provinces from CIHI[5]: The formulary data contain information on all drugs covered by the publicly-funded drug benefit programs in each province and track their formulary coverage start and end dates. The formulary data provides the following main data items for each drug that we used: DIN, CIHI brand generic code which indicates whether a drug is a brand, generic or biologic, plan/program, formulary coverage start date and end date, the listed price (i.e., "the unit price that is accepted as the market price or manufacturer list price" and "subject to plan policies and/or defined under the price reimbursement policy"), if available. "CIHI ensures that the quality of information in our data holdings is suited to its intended uses and that data users are provided with accurate information about data quality".[5] These data fields were extracted by Daphne Guh from the formulary data from April 2008 to March 31, 2017. The formulary data were requested from CIHI by Wei Zhang and the data request information can be found on their website.[5] It was not conducted in duplicate.

4. **PharmaClik:** It is McKesson Canada's internet-based ordering management system that allows pharmacies to place and manage their orders and returns online. McKesson Canada is a leading medication distributor for hospitals and community and retail pharmacies in Canada.[6] PharmaClik was used to provide supplementary information on package size for DINs that are available for pharmacies to order. In 2.1% of DINs, we used PharmaClik to supplement the package size information. We validated the PharmaClik data with DPD and there is a high agreement between the two data. A collaborator, Colleen Brady, provided access to the database to facilitate extraction of package size associated with each DIN by our analyst, Daphne Guh. It was not conducted in duplicate.

Study Design

1. All of above databases were merged together by DIN and package code. Our study sample was all DINs marketed in Canada during March 14, 2017 (already marketed) and September 12, 2018 excluding drugs that do not require a prescription (i.e., OCT and "Ethical" products).

2. A "market" includes all DINs with the same active ingredients, dosage form, route of administration and strength, where the capsules and tablets were treated the same and the oral special release forms (including extended release, controlled release, sustained release and delayed release) were treated the same, i.e., interchangeable.

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A DIN was defined to be in shortage if all of its package sizes were reported to be in shortage on the website. A market was defined to be in shortage if all DINs in this market were reported to be in shortage.

References

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