# Factors Associated with Drug Shortages in Canada: A Retrospective Cohort Study

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| More Detailed Keywords: | Drug shortage, Generic manufacturer, Branded manufacturer |
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| Abstract: | Background: Drug shortages are an ongoing concern both in Canada and globally. To monitor the magnitude of the problem, Health Canada since 2017 have required manufacturers to report on drug shortages. This study aimed to identify the factors associated with drug shortages in Canada.<br><br>Methods: Our study sample was all drugs available on the market in March 14, 2017-September 12, 2018 in Canada excluding over-the-counter and ethical drugs. All strengths of the same active ingredient, dosage form and route of administration, regardless of manufacturer, were grouped into a "market". Shortage at the market-level was defined as all dosage strengths being reported in shortage. The factors considered included market structure at baseline, market age, route/dosage form, and Anatomical Therapeutic Chemical classification.<br><br>Results: Among the 2,023 markets included in our analysis, 12.2% markets were reported to be in shortage and the average shortage duration was 107 days (SD=117). Compared with markets with branded manufacturers only, markets with a single generic manufacturer were more likely to be in shortage (odds ratio=1.48, 95% CI (1.01-2.16)) while markets with multiple generic manufacturers were less likely to be in shortage. Markets with complicated routes/dosage forms were more likely to be in shortage than those that were oral solid with regular release. |

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| | Interpretation: Relatively tight profit margins (which occurs with a single generic manufacturer but not typically with a single branded manufacturer) might lead to shortages. Similarly, shortages were more common in markets with small numbers of manufacturers and markets with complicated administration or delivery mechanisms. |
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# Factors Associated with Drug Shortages in Canada: A Retrospective Cohort Study

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**Competing Interests**

Dr Hollis has received compensation for having provided expert reports relating to patent litigation on behalf of Apotex, Evolution, Mylan and Pharmascience. None of these reports are related to the topic of the paper. All other authors declare no conflict of interest.

## Abstract

**Background:** Drug shortages are an ongoing concern both in Canada and globally. To monitor the magnitude of the problem, Health Canada since 2017 have required manufacturers to report on drug shortages. This study aimed to identify the factors associated with drug shortages in Canada.

**Methods:** Our study sample was all drugs available on the market in March 14, 2017-September 12, 2018 in Canada excluding over-the-counter and ethical drugs. All strengths of the same active ingredient, dosage form and route of administration, regardless of manufacturer, were grouped into a "market". Shortage at the market-level was defined as all dosage strengths being reported in shortage. The factors considered included market structure at baseline, market age, route/dosage form, and Anatomical Therapeutic Chemical classification.

**Results:** Among the 2,023 markets included in our analysis, 12.2% markets were reported to be in shortage and the average shortage duration was 107 days (SD=117). Compared with markets with branded manufacturers only, markets with a single generic manufacturer were more likely to be in shortage (odds ratio=1.48, 95% CI (1.01-2.16)) while markets with multiple generic manufacturers were less likely to be in shortage. Markets with complicated routes/dosage forms were more likely to be in shortage than those that were oral solid with regular release.

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shortages were more common in markets with small numbers of manufacturers and markets with complicated administration or delivery mechanisms.

## INTRODUCTION

Shortages of EpiPen for severe allergies,[1–3] opioid drugs,[4–6] and bupropion for mental illnesses[7] have recently made headlines in Canada and globally. Such shortages can have severe consequences for patients and affect health care delivery costs.[8] For example, opioid shortages increase the risk for medication errors (delayed time to analgesia, side effects, etc.) when patients are administered a less familiar alternative, which leads to unnecessary patient suffering and longer hospital stays.[4,9] Drug shortages can even be life-threatening; for example, there is an association between shortages in generic intravenous norepinephrine and increased mortality among patients with septic shock.[10] In addition, drug shortages can aggravate the stress and burden on physicians and pharmacists and increase labour costs when they have to change their practices due to drug shortages.[8,9] Furthermore, a study from the United States (US) has found that prices increase after drug shortages.[11] In the United Kingdom, after one of the generic manufacturers stopped producing buprenorphine, amid fears of an impending shortage, the government allowed generic versions of this drug to be dispensed at the price of the branded product (i.e. a 700% spike in price).[5]

Many of the reported reasons for drug shortages include manufacturing quality issues, regulatory issues, availability of active ingredients, and the increasing demand for medicines.[8,12–14] Furthermore, researchers and policy-makers have identified underlying factors such as single source product or concentrated markets, and the low price of generic drugs at which generic manufacturers are able to continue producing profitably.[8,12,13] There are several empirical studies that identify the underlying causes of the shortages for generics, vaccines, and injectable drugs.

These studies indicate that in the US, manufacturing-quality problems,[15,16] declines in the number of suppliers,[16] and lower generic drug prices[17–19] are all possible causes.

The bulk of the existing empirical studies on drug shortages were conducted in the US because of the availability of longitudinal, high-quality information on drug shortages on the website of the Food and Drug Administration (FDA)[20] and website of American Society of Health-System Pharmacists.[21] In Canada, while the voluntary reporting of drug shortages goes back to 2011, the response from manufacturers was slow and incomplete until mandatory reporting was implemented on March 14, 2017.[22–25] Despite the fact that Health Canada and researchers have recognized the negative impact of drug shortages on patients, health care professionals and the health care system, the empirical evidence on the major factors associated with drug shortages in Canada is sparse.[12,22,23,26]



## METHODS

### Study Data and Sample

Drug shortage information starting from March 14, 2017 (mandatory reporting) to September 12, 2018 (about 18 months) was extracted from the Canadian Drug Shortage website.[24] The national list comprises manufacturer-reported shortages in the drug manufacturing phase. A pharmaceutical company that knows that they will experience important delays in supplying the Canadian market with an approved drug is required to report it as a ‘drug shortage’ in the Canadian Drug Shortage Database. The database contains information on the specific package code of a drug identification number (DIN) that is in shortage, shortage start date, shortage reasons, and actual or expected shortage end date, where DIN is a unique number to indicate a

drug's active ingredients, strength, dosage form, route of administration and manufacturer while the package code distinguishes different package sizes for each DIN.

In addition to the drug shortage database, other data sources include the Health Canada Drug Product Database (DPD)[27] and pharmacy ordering data from PharmaClick, a drug wholesaler. The DPD contains detailed drug information on all drugs that are available in Canada, which includes each DIN's active ingredients, strength, dosage form, route of administration, manufacturer, package code, Anatomical Therapeutic Chemical (ATC) classification, schedule (prescription, over the counter (OTC), Ethical, Controlled Drugs and Substances Act (CDSA), Biological, etc.), and market status (marketed, cancelled, dormant). Details on definitions of each term can be found on the website.[28] PharmaClick provides supplementary information for the drugs that are available for pharmacies to order.

Our study sample was all DINs marketed in Canada from March 14, 2017 to September 12, 2018 excluding the schedule of OTC and ethical drugs. The follow up time period of each DIN was its time on the market during the study period. DINs with the same active ingredients, dosage form and route of administration were then organized into a group, called a "market".

**Main Outcome and Factors**

Our main outcome is the indicator of a drug shortage at the market level. A market is defined to be in "shortage" if all dosage strengths in a market and all of their package sizes were reported to be in shortage. The shortage duration was then defined as the duration that the entire market was in shortage.

We considered the following factors potentially associated with drug shortages at the market level: 1) market structure (i.e. branded manufacturers only; branded manufacturers and a single generic manufacturer; branded manufacturers and multiple generic manufacturers; biologics; a single generic manufacturer only; and, multiple generic manufacturers) at baseline where baseline was defined as first 30 days of follow-up period; 2) market age at start of follow up (< 5 years, ≥ 5 years); 3) route/dosage form (injection, oral non-solid, oral solid special release, oral solid regular release, other route/form (such as topical cream/ointment, ophthalmic solution, inhalation solution, inhalation power, transdermal patch, nasal spray, etc.)); and, 4) Anatomical Therapeutic Chemical (ATC) classification.

The Canadian Drug Shortage Database includes reasons for the shortage, as reported by manufacturers. Manufacturers can select from the following: shortage of an active or 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, manufacturers can comment on other reasons and based on their comments, we categorized them into either one of the above reasons or into insufficient supply, business or economic reasons, or others/unknown. In our analysis of the shortage duration among those markets in shortage, we further defined the reasons at market level and considered the reasons as one potential factor associated with shortage duration. The reported reason was used when all DINs in the market in shortage were due to the same reason; however, when more than one reason was indicated, we defined it as “multiple reasons”.

**Analyses**

The proportion of markets in shortage and the duration of shortages at the market level among those in shortage were summarized according to specific factors. The association between the factors and drug shortages at market level was assessed using a logistic regression model. The shortage duration was examined using a zero-truncated negative binomial regression model. Sensitivity analyses were conducted by defining "market" by active ingredients only.

**RESULTS**

Our analysis consisted of 2,023 markets (10,067 DINs). Of them, 12.2% markets (n=246) were reported in shortage and the average number of days in shortage was 107 (standard deviation (SD): 117) and median number of days in shortage was 67 (Q1=26, Q3=142). Markets with a single generic manufacturer had the highest proportion (25.5%) of shortage with mean shortage duration of 132.9 days (SD=126.2) (Table 1). Markets that are more complex with respect to route/form were more likely to be in shortage and have a longer shortage duration: 23.0% (112.4 days) for "other complex form/route" vs. 19.2% (107.1 days) for oral non-solid vs. 6.2% (87.1 days) for regular oral solid. Markets that have been in existence for 5 years or longer were more likely be in shortage (13.8% vs 4.2%), and markets of drugs for sensory organs were most likely to be in shortage (30.6% in shortage for a mean 120.9 days).

The multivariate logistic regression results in Table 2 show that compared with markets with branded manufacturers only, markets with a single generic manufacturer were more likely to be in shortage (odds ratio (OR)=1.48; 95% confidence interval (CI) 1.01, 2.16) while markets with multiple generic manufacturers with or without branded manufacturers were 92% or 66% less

likely to be in shortage, respectively. Older markets (on market ≥ 5 years) were four times more likely to be in shortage (OR=4.08; 95% CI 2.43, 7.11)) than markets less than 5 years old. Markets with complex routes/dosage forms (oral non-solid (OR=2.15; 95% CI 1.25, 3.71) and other complicated routes/forms (OR=2.51; 95% CI 1.50, 4.22)) were more likely to be in shortage than those of the oral solid regular release. The sensory organ ATC class was mostly likely to be in shortage. In a secondary analysis, we used a different definition of the market (i.e., a group of DINs with the same active ingredients) and our results were similar (Appendix Table 1).

Appendix Table 2 presents the corresponding reasons for 5,268 shortage incidents reported by manufacturers. A disruption of the manufacture of the drug, a delay in shipping, and an increase in demand for the drug were reported most frequently as the cause of the shortage. We further examined factors (including the aggregated reasons at the market level) associated with the duration of shortage among those markets in shortage (Table 3). Market age and route/dosage form were not significantly associated with shortage duration and thus not included in our final regression model. We found that markets with a single generic manufacturer tended to have a longer duration of shortage than markets with branded-manufacturers only. Markets in shortage due to a demand increase or a compliance issue with the manufacturing process were of the shortest duration while the markets that were in shortage due to disruption in the manufacture of the drug, shortage of ingredient(s) or business or economic reasons had longer duration.

## INTERPRETATION

Our study focused on drug shortages at the market level i.e., all drugs with the same active ingredients, routes of administration and dosage forms were in shortage. Our main finding was that the markets with a single generic manufacturer were the most vulnerable, i.e., associated with a higher odds of a drug shortage. This suggests that relatively low profit margins (which occurs with a single generic manufacturer but not typically with a single branded manufacturer) may lead to shortages. Furthermore, markets with fewer suppliers (i.e., markets with branded only or with single generic manufacturer only) were more vulnerable to shortages. In addition, in our exploratory analysis, we found no shortages occurring in the markets ≤ 2 years and in our final analysis using 5 years as the cut-off, we still found fewer shortages in newer markets, which suggests that manufacturers pay more attention to their supply of the relatively newer products than older products. Another possible reason for older markets having more shortages is that provincial governments restrict price increases for drugs.[29] The markets with complicated routes or formulations requiring complicated manufacturing processes were more susceptible to shortages than oral solid regular release drugs although the generic pricing regulations have been allowing a higher reimbursement price for non-oral solid drugs.[30,31] In terms of shortage duration, the disruption in the manufacture of the drug, shortage of ingredient(s) or business or economic reasons were associated with a longer duration.

Our study is among the first that examines the underlying factors associated with drug shortages. Some of our study findings are consistent with those from the US Government Accountability Office who identified all factors (a decline in the number of suppliers, not complying with manufacturing standards, and drugs with sales of a generic version) that were strongly associated

with shortages of sterile injectable anti-infective and cardiovascular drugs in 2012-2014 in the US.[16] Dave et al. found that special formulations such as solutions and extended-release capsules were associated with higher risks of generic drug shortages in the US.[19] Donelle et al. were the first to assess drug shortage problem using the Canadian drug shortage database.[23] However, their analyses were based on the data reported between 2010 and 2017 (prior to the mandatary reporting), which were incomplete and inaccurate.

Compared with previous studies, one of our study's strengths is that we focused on shortages at the market level rather than at DIN or drug product level. This perspective is more relevant as it speaks to real shortage scenarios as opposed to a situation in which one manufacturer is not supplying but others are. The latter impacts patients less as they can switch brands, or even dosage forms, if necessary to ensure continued therapy. In addition, we considered all active drugs in Canada that can be used in both community and hospital settings instead of focusing on generic drugs for outpatient use only[19] or drugs for certain diseases.[16–18]

Our study did not explicitly consider price as a factor. While lower prices have been found to be associated with shortages of generic drugs,[16] generic sterile injectable drugs,[17] and vaccines,[18] these results are not comparable or relevant to our setting as our study focused on market level and not on specific drug versions. Given that we defined a shortage as when all versions were in shortage, comparing prices across different types of drug markets is not meaningful. Typically, prices for branded, generic, and biologic drugs are determined through different mechanisms and regulated by different pricing policies. In Canada, prices of generic drugs covered under publicly funded insurance programs have been regulated by pan-Canadian tiered pricing framework or by

the provincial price-cap policies,[30,31] under which generic prices are capped at specified percentages of the associated branded drug's price. For patented branded drugs, their prices are regulated by the Patented Medicine Prices Review Board,[32] assessed for cost-effectiveness by the Canadian Agency for Drugs and Technologies in Health,[33] and negotiated by the pan-Canadian Pharmaceutical Alliance.[34] Furthermore, drugs dispensed in hospitals are often purchased and negotiated by group purchasing organizations (GPOs). Thus, to explore the impact of price on drug shortages is beyond the scope of this study.

Our study has important policy implications on how to prevent shortages. First, drug policies should focus not only on price, but also on drug supply security. We know that procurement through GPOs or highly regulated generic pricing (price-capping) policies have been found to discourage manufacturers from supplying drugs and lead to drug company exits,[35–39] often resulting in more concentrated markets and perhaps eventually drug shortages. In this context, some have advocated for the creation of not-for-profit pharmaceutical manufacturing as a solution.[23] For example, to address shortages and high prices of lifesaving medications, a new non-profit generic drug company, Civica Rx, has been established in the US.[40] If Canadian provincial or federal governments were to explore a similar set-up, they would be well advised to focus on drugs with single suppliers especially the single generic manufacturer, complicated routes/formulations, and in certain ATC classifications such as sensory organs. However, we are not advocating the formation of such a state-owned enterprise.

Finally, policy makers trying to balance cost-containment with security of drug supply should be on the lookout for markets with relatively tight profit margins, under pressure of price-capping

policies, resulting in a market with a single generic supplier for a drug with a complex administration or delivery mechanism.

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**Table 1. Markets in shortage and shortage duration**

| Variable<br>Variable Level | Total N | Markets in Shortage N (%) | Shortage Duration among shortage Mean days (SD) |
|---|---|---|---|
| Market Type | | | |
| B Only | 793 | 118 (14.9%) | 82.7 (91.5) |
| B/G Single | 122 | 15 (12.3%) | 137.5 (137.9) |
| B/G Multiple | 324 | 5 (1.5%) | 79.0 (66.4) |
| Biologic | 361 | 35 (9.7%) | 103.6 (125.2) |
| G Multiple | 188 | 13 (6.9%) | 187.3 (190.3) |
| G Single | 235 | 60 (25.5%) | 132.9 (126.2) |
| Route/form | | | |
| Injection | 684 | 74 (10.8%) | 115.0 (131.0) |
| Oral Non-Solid | 156 | 30 (19.2%) | 107.1 (124.9) |
| Oral Solid Regular Release | 694 | 43 (6.2%) | 87.1 (99.3) |
| Oral Solid Special Release | 97 | 9 (9.3%) | 74.3 (82.0) |
| Other | 392 | 90 (23.0%) | 112.4 (114.9) |
| Market Age | | | |
| < 5 years | 354 | 15 (4.2%) | 131.7 (124.7) |
| ≥ 5 years | 1669 | 231 (13.8%) | 105.1 (117.1) |
| Anatomical Therapeutic Chemical classification | | | |
| Alimentary tract and metabolism | 185 | 12 (6.5%) | 89.1 (65.4) |
| Blood and blood forming organs | 85 | 4 (4.7%) | 68.3 (39.8) |
| Cardiovascular system | 170 | 15 (8.8%) | 78.8 (91.3) |
| Dermatologicals | 114 | 22 (19.3%) | 104.4 (132.4) |
| Genito-urinary system and sex hormones | 121 | 17 (14.0%) | 75.7 (65.4) |
| Systemic hormonal preparations, excluding sex hormones and insulins | 67 | 10 (14.9%) | 133.9 (193.3) |
| Anti-infectives for systemic use | 301 | 42 (14.0%) | 138.5 (144.4) |
| Antineoplastic and immunomodulating agents | 254 | 18 (7.1%) | 87.9 (110.8) |
| Musculoskeletal system | 75 | 10 (13.3%) | 169.2 (162.3) |
| Nervous system | 298 | 25 (8.4%) | 122.2 (143.2) |
| Antiparasitic products, insecticides and repellents | 9 | 2 (22.2%) | 62.0 (55.2) |
| Respiratory system | 117 | 24 (20.5%) | 78.3 (58.9) |
| Sensory organs | 111 | 34 (30.6%) | 120.9 (103.0) |
| Various | 116 | 11 (9.5%) | 49.9 (33.0) |

B: branded manufacturers; G: generic manufacturer

**Table 2. The association between factors and the shortage at market level**

| Parameter | Parameter level | OR (95% CI) |
|---|---|---|
| Market type | B/G Single | 0.62 (0.34, 1.12) |
| | B/G Multiple | 0.08 (0.03, 0.21) |
| | G single | 1.48 (1.01, 2.16) |
| | G multiple | 0.34 (0.18, 0.63) |
| | Biologic | 0.82 (0.49, 1.39) |
| | B only | 1.00 |
| Market age | ≥ 5yr | 4.08 (2.34, 7.11) |
| | < 5yr | 1.00 |
| Route/form | Injection | 1.54 (0.96, 2.48) |
| | Oral Non-Solid | 2.15 (1.25, 3.71) |
| | Oral Solid Special Release | 1.58 (0.72, 3.48) |
| | Other | 2.51 (1.50, 4.22) |
| | Oral Solid Regular Release | 1.00 |
| Anatomical Therapeutic Chemical classification | Alimentary tract and metabolism | 1.55 (0.47, 5.11) |
| | Cardiovascular system | 2.86 (0.87, 9.36) |
| | Dermatologicals | 2.49 (0.75, 8.26) |
| | Genito-urinary system and sex hormones | 3.10 (0.96, 9.97) |
| | Systemic hormonal preparations, excluding sex hormones and insulins | 2.59 (0.75, 8.97) |
| | Anti infectives for systemic use | 3.39 (1.15, 10.00) |
| | Antineoplastic and immunomodulating agents | 1.81 (0.58, 5.63) |
| | Musculoskeletal system | 4.14 (1.17, 14.65) |
| | Nervous system | 2.09 (0.67, 6.50) |
| | Antiparasitic products, insecticides and repellents | 6.70 (0.93, 48.27) |
| | Respiratory system | 3.56 (1.11, 11.38) |
| | Sensory organs | 5.35 (1.65, 17.32) |
| | Various | 1.78 (0.54, 5.88) |
| | Blood and blood forming organs | 1.00 |

B: branded manufacturers; G generic manufacturer; OR: Odds Ratio; CI: Confidence Interval

**Table 3. The association between factors and the duration of shortage at market level among those with shortages**

| Parameter | Parameter level | Estimate | SE | P value |
|---|---|---|---|---|
| Market type | B/G Single | 0.120 | 0.329 | 0.715 |
| | B/G Multiple | -0.369 | 0.548 | 0.501 |
| | G single | 0.375 | 0.191 | 0.051 |
| | G multiple | -0.063 | 0.347 | 0.855 |
| | Biologic | 0.348 | 0.230 | 0.132 |
| | B only | 0.000 | 0.000 | |
| Reason | Disruption of the manufacture, shortage of ingredient or business reason | 1.222 | 0.245 | <.0001 |
| | Delay in shipping or insufficient supply | 0.230 | 0.289 | 0.425 |
| | Multiple or other reasons | 0.543 | 0.267 | 0.043 |
| | Demand increase or requirements related to complying with good manufacturing practices | 0.000 | 0.000 | |

B: branded manufacturers; G generic manufacturer; SE: Standard Error

**Appendix Table 1. The association between factors and the shortage at market level**

| Parameter | Parameter level | OR (95% CI) |
|---|---|---|
| Market type | B/G Single | 0.78 ( 0.37 , 1.64) |
| | B/G Multiple | 0.06 ( 0.02 , 0.20) |
| | G single | 2.00 ( 1.10 , 3.62) |
| | G multiple | 0.35 ( 0.15 , 0.83) |
| | Biologic | 1.04 ( 0.55 , 1.98) |
| | B only | 1.00 |
| Market age | ≥ 5yr | 3.20 ( 1.69 , 6.08) |
| | < 5yr | 1.00 |
| Route/form | Injection | 1.61 ( 0.87 , 2.97) |
| | Oral Non-Solid | 2.71 ( 1.06 , 6.92) |
| | Oral Solid Special Release | 1.24 ( 0.35 , 4.40) |
| | Other | 2.84 ( 1.35 , 6.00) |
| | Oral Solid Regular Release | 1.00 |
| Anatomical Therapeutic Chemical classification | Alimentary tract and metabolism | 1.59 ( 0.37 , 6.72) |
| | Cardiovascular system | 3.81 ( 0.95 , 15.35) |
| | Dermatologicals | 1.47 ( 0.31 , 7.08) |
| | Genito-urinary system and sex hormones | 3.50 ( 0.87 , 14.14) |
| | Systemic hormonal preparations, excluding sex hormones and insulins | 4.73 ( 1.10 , 20.34) |
| | Anti infectives for systemic use | 3.99 ( 1.14 , 14.00) |
| | Antineoplastic and immunomodulating agents | 2.08 ( 0.56 , 7.73) |
| | Musculoskeletal system | 6.85 ( 1.56 , 30.20) |
| | Nervous system | 1.49 ( 0.35 , 6.36) |
| | Antiparasitic products, insecticides and repellents | 8.69 ( 1.07 , 70.71) |
| | Respiratory system | 2.78 ( 0.65 , 11.88) |
| | Sensory organs | 10.44 ( 2.54 , 42.99) |
| | Various | 2.28 ( 0.56 , 9.33) |
| | Blood and blood forming organs | 1.00 |

B: branded manufacturers; G generic manufacturer

## Appendix Table 2. Reasons reported for drugs in shortage

| Reason | All | Branded | Generic | Biologic | Injection | Ora Non-solid | Oral Solid Regular Release | Oral Solid Special Release | Other routes/forms |
|---|---|---|---|---|---|---|---|---|---|
| Disruption of the manufacture of the drug | 2755 (58.1%) | 263 (36.1%) | 2475 (63.6%) | 17 (13.8%) | 201 (38.3%) | 82 (73.9%) | 1991 (61.8%) | 264 (60.0%) | 217 (48.8%) |
| Demand increase for the drug | 447 (9.4%) | 117 (16.1%) | 295 (7.6%) | 35 (28.5%) | 99 (18.9%) | 14 (12.6%) | 253 (7.8%) | 42 (9.5%) | 39 (8.8%) |
| Delay in shipping of the drug | 878 (18.5%) | 159 (21.8%) | 681 (17.5%) | 38 (30.9%) | 106 (20.2%) | 6 (5.4%) | 590 (18.3%) | 88 (20.0%) | 88 (19.8%) |
| Requirements related to complying with good manufacturing practices | 158 (3.3%) | 14 (1.9%) | 125 (3.2%) | 19 (15.4%) | 40 (7.6%) | 2 (1.8%) | 85 (2.6%) | 16 (3.6%) | 15 (3.4%) |
| Insufficient supply | 96 (2.0%) | 13 (1.8%) | 81 (2.1%) | 2 (1.6%) | 11 (2.1%) | 0 (0.0%) | 74 (2.3%) | 7 (1.6%) | 4 (0.9%) |
| Shortage of an active/inactive ingredient or component | 144 (3.0%) | 37 (5.1%) | 107 (2.7%) | 0 (0.0%) | 20 (3.8%) | 2 (1.8%) | 102 (3.2%) | 7 (1.6%) | 13 (2.9%) |
| Business or economic reasons | 50 (1.1%) | 7 (1.0%) | 43 (1.1%) | 0 (0.0%) | 4 (0.8%) | 3 (2.7%) | 31 (1.0%) | 7 (1.6%) | 5 (1.1%) |
| Others/unknown | 216 (4.6%) | 118 (16.2%) | 86 (2.2%) | 12 (9.8%) | 44 (8.4%) | 2 (1.8%) | 97 (3.0%) | 9 (2.0%) | 64 (14.4%) |

The reasons were summarized at shortage report level

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

| | Item No | Recommendation | Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract<br>(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | Title<br>P3 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | P5 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | P6 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | P6 and P7 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | P6 and P7 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>(*b*) For matched studies, give matching criteria and number of exposed and unexposed | P6 and P7<br>N/A |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | P7 and P8 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | P6-P8 |
| Bias | 9 | Describe any efforts to address potential sources of bias | P9 |
| Study size | 10 | Explain how the study size was arrived at | P7 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | P8 and P9 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding<br>(*b*) Describe any methods used to examine subgroups and interactions<br>(*c*) Explain how missing data were addressed<br>(*d*) If applicable, explain how loss to follow-up was addressed<br>(*e*) Describe any sensitivity analyses | P9 |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed<br>(b) Give reasons for non-participation at each stage<br>(c) Consider use of a flow diagram | P9 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders<br>(b) Indicate number of participants with missing data for each variable of interest<br>(c) Summarise follow-up time (eg, average and total amount) | P9 and Table 1 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | P9 |

| | | | |
|---|---|---|---|
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>(*b*) Report category boundaries when continuous variables were categorized<br>(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | P9 and P10; Tables 2 and 3 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | Appendix Tables 1 and 2 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | P11 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | P12 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | P11-P13 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | P11 and P12 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | P1 |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.