# Drug shortages. Part 2

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INVITED REVIEW

# Drug shortages. Part 2: Trends, causes and solutions

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## Abstract

Drug shortages make it difficult or impossible to meet the therapeutic needs of individual patients or populations. In the first part of this review we proposed an operational definition that incorporates the processes by which products are manufactured, the causes of shortages and stock-outs (local shortages), and the contributory factors. Here we discuss causes and possible solutions. Drug shortages have complex causes, and a single cause cannot always be identified. Reasons include lack or shortage of raw materials, manufacturing difficulties, regulatory and political actions, voluntary recalls, just-in-time inventory systems, halts in production for financial or other business reasons, low demand (eg, orphan products, reduced usage), mergers, market shifts (eg, diversion to home markets) and unexpected increases in demand (eg, improved diagnosis, new trial information, epidemics and pandemics, inappropriate use, off-label use). Potential solutions are as diverse as the potential causes. Prevention is hard, because shortages are not easily predicted. Everyone in the supply chain is involved in anticipating and managing shortages, with responsibilities for preventing them or at least trying to mitigate their effects. This includes manufacturers and suppliers, particularly of generic formulations, pharmacists, prescribers, patients and governments. Solutions can therefore be linked to the causes and classified according to where the responsibility for implementing them lies.

KEYWORDS
adverse reactions, medication errors, pharmaceutical preparations, prescription drugs, shortages

## 1 | INTRODUCTION

In the first part of this two-part review on drug shortages, we discussed how drug shortages are defined and the harms, including medication errors, that can result. In this second part, we shall discuss the trends in drug shortages, their causes and potential solutions.

## 2 | TRENDS IN DRUG SHORTAGES

Ignoring the Dutch shortage of leeches in the early 19th century,[1] early examples of documented medical shortages include bedpans in 1900,[2] medical officers in 1906,[3] catgut in 1916,[4] industrial platinum in 1917[5] and helium in 1927.[6] Most referred to staff shortages—doctors, nurses, domestic help, chemists—and in one case shortages of

subjects for anatomical dissection.[7] Shortages of dietary calcium[8] and hospital beds[9] also featured.

Reports of shortages of medicinal products appeared during both World Wars and intermittently in between. Sporadic reports then appeared until the 1990s, after which there was a small gradual increase. In 2004-2005, a small peak was mainly caused by shortage of a single product, influenza vaccine, but in 2011-2012 there was a sudden major increase followed by a partial recovery. In 2018-2020 there was a further marked increase, which appears to have been sustained to date.

In 2018, for example, French regulators managed 871 shortages, compared with 405 in 2016,[10] while there were 769 shortages in the Netherlands.[11] In 2019 Australia prescribers faced critical shortages of 56 medicines,[12] around 5% of licensed medicinal formulations were unavailable in Belgium[13] and in the United States 213 products were in short supply.[14] In the United Kingdom, over 900 formulations have been in short supply since 2014 for periods of weeks to months, some indefinitely.[15] Shortages have also occurred during the recent pandemic,[16] and shortages continue to be reported from time to time worldwide. Recent examples include shortages of 30 brands of hormone replacement therapy (HRT),[17,18] of temazepam[19,20] and of amoxicillin.[21,22]

The time course of publications listed in PubMed referring to drug shortage(s) from 1990 to 2022 is plotted in Figure 1.

The increase in the numbers of shortages in 2011-2012 (Figure 1) may have been, at least in part, triggered by the financial crisis of 2007-2008, after which several generics companies ceased trading, followed by partial recovery. Increasing use of the "just-in-time" inventory system, in which companies order raw ingredients only in amounts sufficient to meet imminent expected demand, which must therefore be accurately gauged, may also have contributed. The reasons for the recent major increase are not clear, but the covid-19 pandemic has probably been a contributory factor.[23–25] However, individual shortages have had widely differing causes, many of which would have been unpredictable, and the solutions to which have been widely diverse.

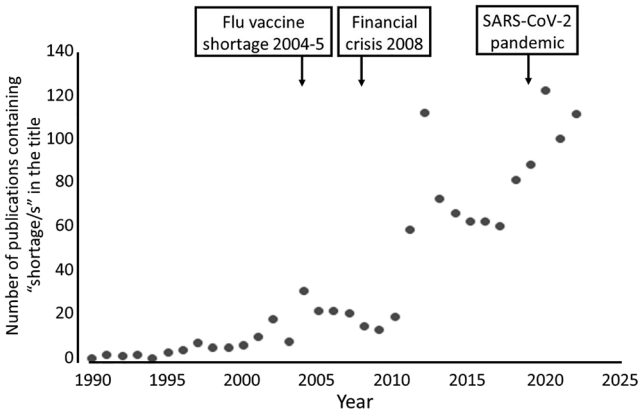


**FIGURE 1** Numbers of publications 1990-2022 containing the term "shortage/s" in their titles and dealing with shortages of medications (source PubMed). "Medications" includes pharmaceutical products, vaccines, oxygen and products for parenteral nutrition, but not blood products, radiocontrast media or radionuclides.

## 3 | CAUSES OF DRUG SHORTAGES

The causes of shortages of medicines are complex. A single cause cannot always be identified, and sometimes the reasons cannot be fully

**TABLE 1** Causes of shortages of medicinal products.

| Cause | Examples |
|---|---|
| Lack of raw materials (eg, due to difficulties with animals, contamination, impaired plant or tissue growth, conflicts, natural disasters such as hurricanes and tsunamis) | Isoprenaline (unspecified shortage of raw materials)[26]; heparin (limited animal supply)[27]; immunoglobulin (contamination with CJD)[28]; ranitidine (contamination with a carcinogenic impurity)[29]; growth hormone (reduced mortuary supply of pituitary glands and over-optimism about the availability of the hormone from genetically engineered bacteria)[30]; mepacrine (unavailable from wartime Germany)[31] |
| Shortage after glut | Quinine[31] |
| Technical difficulties in manufacture | Intravenous immunoglobulin; influenza vaccine[32] |
| Regulatory action (eg, shutting down a factory because of poor manufacturing practices, stricter quality criteria, legalization) | Cannabis (increased demand after legalization)[33]; testosterone (poor manufacturing quality)[34]; streptomycin (Global Drug Facility quality criteria)[35] |
| Voluntary recalls (eg, because of concerns about quality or harms) | *Haemophilus influenzae* type b (Hib) conjugate vaccines[36] |
| Just-in-time inventory systems (see text) | Antimicrobial drugs[37] |
| Halt in production for financial or other business reasons | Spectinomycin (reduced demand)[38] |
| Low demand (eg, orphan products, reduced usage) | Imiglucerase (orphan drug)[39]; selegiline (reduced use leading to reduced production)[40] |
| Mergers | Intravenous sodium bicarbonate (reduced to a single supplier)[41] |
| Supply diverted | Albumin diverted to battle zones during Desert Storm[42] |
| Unexpected increases in demand (eg, improved diagnosis, epidemics, inappropriate use, off-label use) | Alpha 1-proteinase inhibitor (increased demand from increased diagnosis)[43]; hydroxychloroquine (inappropriate and off-label use during a pandemic)[44]; intravenous immunoglobulin (off-label use)[45]; proton pump inhibitors (inappropriate use)[46]; steroid inhalers during covid-19 (increased demand)[47]; yellow fever vaccine[48]; semaglutide (off-label use in obesity)[49] |
| Political actions (eg, embargos) | Opiates (prohibited production in Turkey)[50] |

comprehended. Table 1 documents the many reasons for shortages of medicinal products found in reviewing the published literature, 1297 papers in all, with examples.[26–50]

## 4 | SOLUTIONS

Because the causes of drug shortages are multifarious, many solutions have been proposed.

### 4.1 | Predictable causes

Prevention of shortages is the ideal, and prevention is possible when shortages are predictable. For example, a company that takes over another may abandon its products. Companies intending takeovers should give warning about such possibilities and highlight the products that are likely to be affected.

In New Zealand, the Government, through its Pharmaceutical Management Agency (PHARMAC), which was established in 1993, makes contracts with pharmaceutical companies requiring them to notify the Agency when stocks fall below a certain level and requiring suppliers to pay to cover the cost of a replacement product.[51] When a shortage takes the market by surprise, PHARMAC works closely with suppliers and obtains clinical advice to ensure that suitable alternatives can be sourced. When a pharmaceutical supplier signs a contract with PHARMAC they accept responsibility to maintain supply. PHARMAC claims that because of this approach New Zealand experiences comparatively fewer supply issues than most other countries. However, New Zealand sales represent only 0.1% of the global pharmaceutical market, and whether this approach would work in larger markets is not clear.

### 4.2 | Unpredictable causes

In many cases, however, shortages cannot be prevented because the causes are unpredictable, such as natural disasters, conflicts and governmental diktats, difficulties with animals, impaired plant growth and contamination, bacterial or chemical.

Some medicinal products, for example, may be needed infrequently and needs are not easy to predict; examples include dantrolene injection in the emergency treatment of malignant hyperthermia, on which guidelines are available,[52] and oseltamivir, whose stockpiling in anticipation of an influenza epidemic is widely recommended, but whose benefit to harm balance may be unfavourable.[53]

Concerns over the quality of a product can lead a manufacturer to stop production or a regulator to close down a production plant. A financial crisis can lead to closures, which may have at least partly explained the sudden major increase in shortages in 2011-2012 following the financial crisis of 2008-2009. Such events are often unpredictable.

Expiry dates of medicinal products are highly conservative and underestimate the shelf lives of many products[54]; they could be extended, although there are problems in deciding by how much. In 2006 the US Shelf Life Extension Program (SLEP) reported that 2650 (88%) of 3005 lots of 122 different medicinal products stored in their unopened original containers remained stable for an average of 66 months after the expiry date; 312 lots (10%) remained stable for more than 4 years.[55] However, failures arose in 479 lots (16%) from loss of potency, the presence of impurities or changes in pH, water content, dissolution characteristics or physical appearance. Nevertheless, there were no failures within 1 year after expiry. Furthermore, the risks of failures varied with time; for example, diazepam autoinjectors and doxycycline tablets had no failures until the sixth year of testing. These data show how hard it can be to be sure that expiry dates can be extended and for how long. A possible solution would be to mandate repeated stability testing after licensing, so that, year by year, the limit could be increased if appropriate.

In July 2019 the UK Government passed legislation allowing community pharmacists in England to vary the instructions in an individual prescription without consulting the prescriber and to dispense appropriate alternatives to cover serious shortages of medicines under so-called Serious Shortage Protocols.[56] The legislation was first used to extend the expiry date of fluoxetine formulations; the extension lapsed when the shortage resolved.[57] This method of coping with shortages is likely to be used again. It should preferably be limited to relatively short periods of time and apply only to products that are still in their original packaging and have been properly stored.

When shortages occur, substitutes are often used. Me-too drugs may in this way find some use,[58] although there are very few reported instances of this and often substitutes are not me-toos. Adverse reactions to substitutes have also been reported from time to time, when, for example, differences in potency are not recognized. The use of biosimilars[59] when there are shortages of originator molecules has been occasionally discussed.[60]

A similar approach in response to the pandemic has been described in Canada, where the Government announced in 2020 that it would license companies to make generic copies of brand-name products without having to negotiate with patent holders and compensate patent holders after the fact; this was made possible by amendment of the Patent Act under Canada's COVID-19 Emergency Response Act.[61] This seems to have been at least partly effective in reducing shortage rates.[16]

During shortages, limits on dispensing and sales at pharmacies do not solve the problem but make equitable access more likely.[62,63]

In recent years several reports have made recommendations on how to prevent and deal with shortages. The European Medicines Agency (EMA) has prepared documents,[64] including reports from the HMA/EMA Task Force on Availability of Authorised Medicines for Human and Veterinary Use.[65] The US Food and Drug Administration (FDA) has issued a report titled "Drug Shortages: Root Causes and Potential Solutions",[66] on which the Healthcare Supply Chain Association (HSCA) has commented at length.[67] The reports of the Association of Health-System Pharmacists, highlighted in Part 1 of this review, also contain extensive recommendations. There are also provisions in the Food and Drug Administration Safety and Innovation Act (FDASIA; Title X[68]).

**Box 1 Some published recommendations for preventing drug shortages and dealing with them when they occur; we report them here and do not necessarily endorse them**

**(a) Governments should**

*Increase awareness*

- by quantifying the harms that shortages can cause
- by providing better data on actual shortages (frequency, intensity, and duration)
- by informing the public and the news media when shortages are expected or occur, including easily accessed websites

*Require manufacturers*

- to produce risk management plans that cover shortages

*Incentivize manufacturers*

- to produce medicines that are less profitable
- by relaxing regulations when recovery from a shortage is required

*Recognize and reward manufacturers' activities*

- by rating good manufacturing practices, including systems for quality control
- by financial incentives to continue producing older medicines

*Foster the supply of generic medicines*

- by encouraging the establishment of local suppliers
- by establishing national suppliers

**(b) Regulators should**

*Increase awareness*

- by quantifying the harms that shortages can cause
- by providing better data on actual shortages (frequency, intensity and duration)
- by informing the public and the news media when shortages are expected or occur, including easily accessed websites
- by predicting cost implications of shortages
- by ensuring widespread communication with prescribers and patients

*Enable more efficient use of medicines*

- by allowing hospital pharmacists to repackage medicines to share with other hospitals
- allowing pharmacists to substitute alternative formulations, for example 28 tablets of 5 mg rather than 14 tablets of 10 mg, without consultation with the prescriber
- by allowing pharmacists to substitute alternative medicines expected to be equally efficacious and safe, after consultation with the prescriber and patient/carer (Serious Shortage Protocols)
- by monitoring implementation of risk management plans
- by appropriately extending labelled shelf lives

*Anticipate shortages*

- by predicting cost implications of shortages

*Prevent and deal with shortages*

- by having procedures in place for deciding how to use substitutes, for approving them, and for advising about appropriate use and rationing in appropriate patients

*Recognize and reward manufacturers' activities*

- by rating good manufacturing practices, including quality management systems
- by financial incentives to continue producing older medicines

**(c) Manufacturers should**

*Increase awareness*

- by providing better data on actual and anticipated shortages (frequency, intensity and duration)
- by informing the public and the news media when shortages are expected or occur, including easily accessed websites
- by warning about expected difficulties in supply as soon as possible, including assessment of the impact of the expected shortage (see the EMA's proposed template for shortage notification)
- by providing the regulator with information on the volume of sales of the medicinal product when asked

*Anticipate shortages*

- by producing and adhering to risk management plans
- by warning about takeovers well in advance and specifying medicines whose production may be stopped
- by stocking larger amounts of production materials and finished products (ie, mitigating the "just-in-time" policy)
- by recording and reviewing all complaints about quality and the need to recall affected products, and by informing the regulator of any defect detected that could result in a recall or abnormal restriction on supply and the likely countries affected

*Prevent shortages*

- by agreeing to contracts requiring maintenance of supply by ensuring that sufficient supplies will be available for clinical trials before the trials start

**(d) Purchasers should**

*Increase awareness*

- by keeping themselves well informed
- through widespread communication with prescribers and patients

*Prevent shortages*

- by insisting on contracts with manufacturers requiring maintenance of supply
- by financial incentives to manufacturers to continue producing older medicines
- by predicting cost implications
- by avoiding speculative stockpiling

*Be prepared to deal with shortages*

- by having contingency plans for purchasing, storage, preparation and dispensing of the relevant medicine and possible alternatives
- by having procedures in place for deciding on how to use substitutes, for approving them, and for advising about appropriate use and rationing in appropriate patients

*Foster the supply of generic medicines*

- by encouraging the establishment of local suppliers

**(e) Prescribers should**

*Increase awareness*

- by informing patients about shortages, the reasons and possible methods of management

*Make better use of medicines*

- by using me-toos and biosimilars when appropriate
- by collaborating with pharmacists in the case of Serious Shortage Protocols

**(f) Pharmacists should**

*Increase awareness*

- by informing patients about shortages, the reasons and possible methods of management

*Make better use of medicines*

- by dispensing medicines beyond stated expiry dates (empowered by regulators and in collaboration with prescribers)
- by avoiding speculative stockpiling

Various published recommendations are summarized in Box 1. Some of these recommendations are directly related to causes and can be mapped onto the causes of drug shortages by linking them to the information given in Table 1 and the operational definition shown in Figure 1 in Part 1 of this review. For example, a shortage caused by reduced drug production following a merger might be prevented or minimized by incentivizing manufacturers to continue manufacturing and marketing a product that they would otherwise have abandoned. Just as the causes of shortages are multifarious, so there may be more than one potential solution. For example, manufacturers intending to stop marketing a product after a merger could give a lead time to allow substitutes to be made available. Other recommendations are designed to increase awareness of the possibility of shortages, allowing time for preventive or mitigating actions to be taken.

## 5 | CONCLUSIONS

Shortages of medicines harm and worry patients, increase the risk of medication errors, and impose administrative and financial burdens on healthcare.

The causes of drug shortages are complex, and some—such as natural disasters—cannot be predicted. When they can be predicted (eg, because a manufacturer plans to cease production), they can and should be mitigated.

When drugs are, in some sense, essential, there is a strong argument for increasing stocks and possibly for assuring domestic manufacture, especially if there are no suitable alternatives. However, the definition of "essential" will vary according to local healthcare requirements and individual patients' views of their needs for treatment.

Everyone in the supply chain is involved in anticipating and managing shortages, with responsibilities for preventing them or at least trying to mitigate their effects. This includes manufacturers and suppliers, particularly of generic formulations, pharmacists, prescribers, patients and governments.

### AUTHOR CONTRIBUTIONS

Jeffrey K. Aronson and Robin E. Ferner performed literature searches. Jeffrey K. Aronson wrote the first draft. All authors contributed to the writing of the final paper.

### CONFLICT OF INTEREST STATEMENT

J.K.A. and R.E.F. have no direct competing interests; they have both written articles and edited textbooks on adverse drug reactions and have acted as expert witnesses in civil and coroners' cases involving such reactions. C.H. holds grant funding from the NIHR, and the NIHR School of Primary Care Research; he has received financial remuneration for legal advice and has received expenses and fees for his media work.

### DATA AVAILABILITY STATEMENT

The results of searches used in this review are available on request from the corresponding author.

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