

**ECONOMIST
IMPACT**

Confronting the Fragility of Medicine Supply Chains



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About this report

Confronting the fragility of medicine supply chains is an Economist Impact report, sponsored by LEO Pharma A/S. The white paper examines the complex causes of disruptions in the supply chains for drugs, with a particular focus on their active pharmaceutical ingredients (APIs). It looks at some of the efforts to mitigate and avoid shortages and suggests some potential structural solutions.

The report is informed by a literature review, three case studies (on piperacillin-tazobactam, heparin and vincristine) and by expert interviews. We would like to thank the following individuals (listed alphabetically) who have contributed their views and insights for this paper:

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- **Maria Badia-Tahull**, Section Head, Pharmacy Department, Hospital Universitari Bellvitge (ICS), Barcelona
- **Lisa Burry**, Clinical Pharmacy Specialist, Mount Sinai Hospital and the University of Toronto
- **Brian Godman**, Professor, Strathclyde Institute of Pharmacy and Biomedical Sciences in Scotland
- **Luis Palomares**, Pulmonologist, Institute of Biomedicine of Seville and University Hospital Virgen del Rocio, Seville
- **Mark Rosenberg**, CEO of justmedicine.org
- **Fiona Scott Morton**, Theodore Nierenberg Professor of Economics at Yale University School of Management

Economist Impact bears sole responsibility for the content of this report. The findings and views expressed in the report do not necessarily reflect the views of the sponsor. The research team consisted of Anelia Boshnakova, Andrea Chipman and Alan Lovell.

Executive summary

The global coronavirus pandemic has spotlighted a number of weaknesses in health systems, but one that has received relatively little attention is regular and ongoing shortages of essential medicines. Disruption of supply chains, in particular for active pharmaceutical ingredients (APIs) — due in part to accelerated, simultaneous demand for medicines such as sedatives and corticosteroids — was a common feature of the pandemic. Yet, the structural and economic circumstances that helped contribute to these problems were in existence well before covid-19 made its first appearance.

The business model of off-patent manufacturers operates on slender profit margins, which has led to consolidation within the industry. This dynamic has helped to create a vicious circle in which supply chains have become extended, largely concentrated in emerging market countries such as China and India, and increasingly vulnerable to external shocks. Purchasers who use tendering processes that elevate price over the resilience of suppliers have exacerbated these trends. Meanwhile, the United States, with its fragmented health system, and the European Union, where health responsibilities are divided between EU bodies and those of member states, face particular challenges in ensuring continuity of medicine supplies.

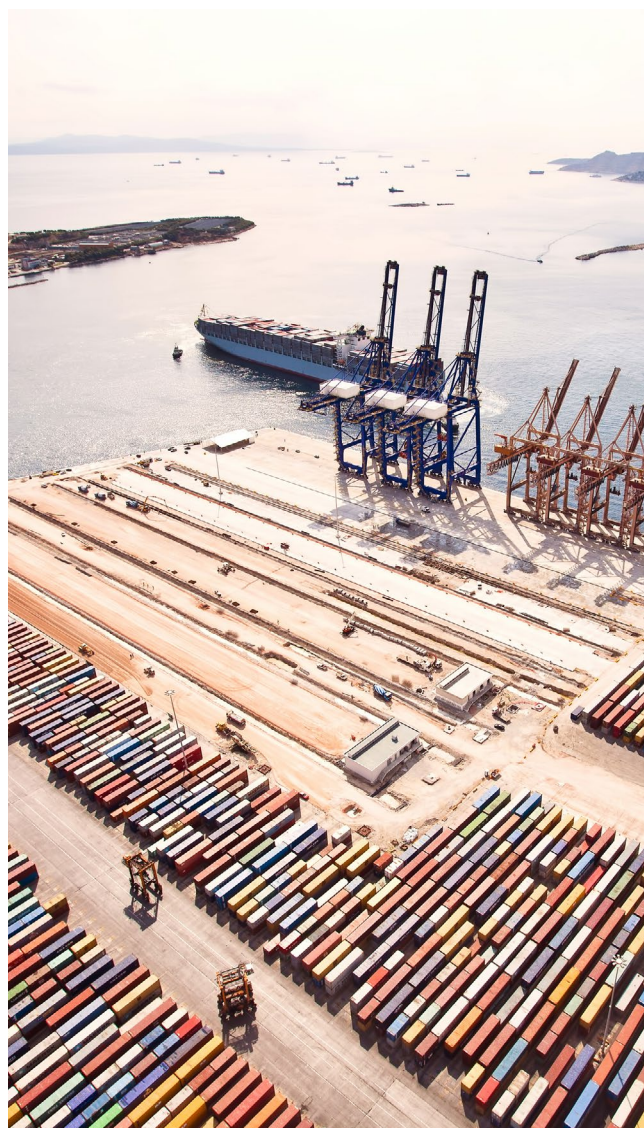
The business model of off-patent manufacturers operates on slender profit margins, which has led to consolidation within the industry. This dynamic has helped to create a vicious circle in which supply chains have become extended, largely concentrated in emerging market countries such as China and India, and increasingly vulnerable to external shocks.

Reducing the threat of API shortages is likely to require a combination of actions from manufacturers, purchasers and governments or regulatory agencies. We suggest that future policies should be built around the following principles:

- **Purchasers need to find ways of aligning incentives.** Off-patent drug producers operating on narrow profit margins have little reason to ensure the reliable supply of raw materials. Creating aligned incentives that focus on resilience rather than the lowest price would help.
- **Better transparency and communication between manufacturers and purchasers is vital.** Producers of APIs need to keep communication lines open so that purchasers will have advanced warning about potential disruptions. In return, purchasers need to be able to give manufacturers as much warning as possible about potential demand spikes.
- **Health systems need to put measures in place to better prepare for shortages.** Better forecasting, whether by regional health officials or hospital pharmacies, could help identify likely demand for essential medicines. Planners could also determine potential alternative medicines to be used in the event of shortages or priority systems for prescribing drugs during scarcity.
- **Drug manufacturers need to ensure multiple sources of APIs.** Declining profitability of certain medicines, industry consolidation and dependence on natural resources to make raw materials for certain medicines have led to a situation where many APIs for an essential medicine are produced by a single company. Drug manufacturers need to work with

each other, and with government or regulatory agencies where necessary, to ensure multiple sources of APIs.

- **Supply chains need to be made shorter.** Concentration of production of APIs in one or two geographical locations, frequently in low- and middle-income countries (LMICs), leaves supply chains especially vulnerable to external shocks. Onshoring of manufacturing may be one solution to this problem.



Chapter 1: Introduction

The past eighteen months of pandemic have been marked by high-profile shortages of necessary medications, which have threatened the health and lives of patients globally.

But this is not a new phenomenon. The problem of disruptions to supplies of raw materials for medicines—and, by extension, periodic shortages of essential drugs—had been growing for many years before the arrival of covid-19. Indeed, medicine procurement officials at hospitals around the globe have faced shortages of essential medicines from corticosteroids to analgesics.

There are structural factors that have set the stage for the current crisis, from the increasing globalisation of the supply chain for essential off-patent medicines to market consolidation. These trends, along with external events such as natural disasters and, most recently, the pandemic, have helped make supplies of the active pharmaceutical ingredient especially vulnerable.

Why is this the case? Experts interviewed for this paper agree that there are structural factors that have set the stage for the current crisis, from the increasing globalisation of the supply chain for essential off-patent medicines to market consolidation. These trends, along with external events such as natural disasters and, most recently, the pandemic, have helped make supplies of the active pharmaceutical ingredient (or “API”, the biologically active component of a drug that produces the intended effect) especially vulnerable.

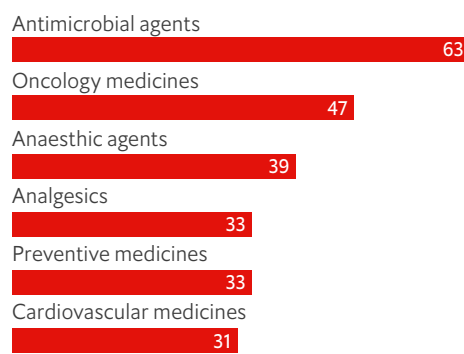
There are many differing perspectives on the cause of drug shortages

The problem of medicine and API shortages has drawn the attention of a number of regulatory agencies and healthcare organisations, yet there remains little evidence about the prevalence and impact of shortages on patient care. The dearth of data led the European Association of Hospital Pharmacists (EAHP) to carry out a series of surveys on medicine supply shortages in the hospital sector over the past decade.¹

The most recent survey in 2019 found that 95% of pharmacists reported that shortages are a major problem in their hospital, compared with 92% in 2018.² The survey—which included not only hospital pharmacists, but also physicians, nurses, other health professionals and patients from 39 countries—identified antimicrobial agents, oncological medicines and anaesthetic agents as the classes of medicines most frequently in short supply (Figure 1). This finding is similar to the conclusions of a 2019 summary from the U.S. Food and Drug Administration (FDA), which found that more than half of all shortages were in sterile injectables, including chemotherapy, anaesthesia and other acute drugs.³

Figure 1: Antimicrobial agents, oncology medicines and anaesthetic agents were seen by hospital pharmacists as the three drug classes most likely to be affected by shortages in European hospitals

%, Respondents could select all that apply

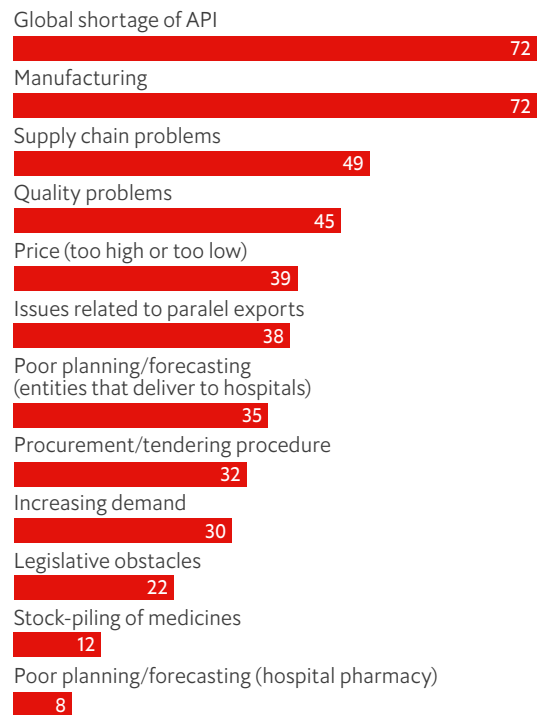


Source: 2019 EAHP Medicines Shortages Report²

There are different perspectives on the reasons for medicine disruptions. Pharmacists cite global API shortages, manufacturing issues and supply chain problems (Figure 2), while physicians responded that the price of medicines is the primary cause.² An FDA report, meanwhile, found quality problems related to manufacturing issues, or delays and capacity problems involving raw materials, to be the main causes of shortages.⁴

Figure 2: Global shortages of active pharmaceutical ingredient were seen by hospital pharmacists as the primary cause of drug shortages in European hospitals

%, Respondents could select multiple reasons.



Source: 2019 EAHP Medicines Shortages Report²

While there is no silver bullet, marketplace reforms will be at the heart of any long-term solution

As this paper will argue, the combination of consolidation within the generics industry and skewed incentives that discourage investment have created an environment in which supply disruptions inevitably happen. The profit margins on most compounds are paper-thin, which is a leading contribution to the lack of resilience built into the operations of many manufacturers. Added to this, a lack of transparency also makes it difficult for manufacturers of final products to identify weaknesses in supply chains, often until it is too late.

Resolving these issues will not be easy. Effective solutions are likely to involve efforts to diversify suppliers and investing more in ensuring capacity and quality. This will increase costs to consumers and manufacturers. Solutions may also involve the establishment of new regulatory bodies or oversight or, in some cases, new requirements for suppliers, overseen by end-users.

The consequences to patients of shortages, however they manifest themselves, are often

severe. Interruptions in treatment or the need for more costly therapies are common problems, resulting in poorer management of medical conditions and adverse medical reactions. And although there may be alternatives to some medicines—such as biosimilars, medicines made from living organisms that are designed to be highly similar to the reference drug they are meant to replace⁵—others have no obvious suitable replacement.

Alongside a thematic review, this paper uses short case studies of three different medications that have been affected by shortages in recent years. The case studies of medicines are selected as examples from three classes of drugs commonly impacted by shortages. As can be seen in **Table 1**, all three are essential drugs for one or more groups of patients. These are not by any means the only drugs for which serious shortages are commonplace. Maria Badia-Tahull, Section Head of the Pharmacy Department at Hospital Universitari Bellvitge, Barcelona, explains how in her hospital pharmacy she currently has ongoing shortages of (among others) a range of immunoglobulins, the antibiotic aztreonam, and the anti-tuberculosis drug rifampicin.

Table 1: Our three case studies of drug shortages, their importance to patients and the main reason(s) for shortages

Medicine	Type	Importance to patients	Major reason for shortage
Vincristine	Chemotherapy	Essential drug for a number of major cancers, including paediatric leukaemia	Less profitable for producers, manufacturing issues including shortages of plant from which main compound is derived
Piperacillin-Tazobactam	Antimicrobial	When patients are forced to use alternatives, there have been documented health effects	Too few manufacturers, geographical concentration
Heparin	Anticoagulant	Required for life-saving surgery where alternatives are less effective; in special demand during covid-19	Swine flu and over-consolidation of market

Chapter 2:

A system with weakness built in

Supply chains for the raw materials making up generic medicines have been increasingly prone to disruptions and shortages over the past decade or so. A 2020 survey by the Pharmaceutical Group of the European Union (PGEU) found that 17 of 26 responding countries reported that medicine shortages had become worse in the past 12 months; in 2019, 22 countries had reported a worsening situation.⁶

The reasons for shortages are many and varied, ranging from an increasingly consolidated industry with razor-thin profit margins, to inflexible regulators, market shocks and natural disasters. As we will see below, these drivers often overlap, leading to a vulnerable ecosystem that is prone to collapse.

“Awarding a drug tender to a single supplier puts it at a high risk of shortage.”

Maria Badia-Tahull, Section Head, Pharmacy Department, Hospital Universitari Bellvitge (ICS), Barcelona

The current system incentivises fragility

Economic factors, especially skewed market and pricing incentives, are often cited as the underlying cause behind many of the shortages discussed in this paper. Indeed, a 2019 report by the FDA found that economic issues were most often responsible for drug shortages and identified three root causes:⁴

1. The lack of incentives for manufacturers to produce less profitable drugs,
2. The absence of recognition or reward for manufacturers that implement “mature quality systems” focusing on continuous improvement
3. Logistical and regulatory challenges that made it difficult for markets to recover from a disruption.

One of the principal reasons for API shortages is the limited numbers of suppliers. This is due to the intense competition between suppliers that has led to industry consolidation, decreasing the number of manufacturers supplying producers of final products as they all compete to be the lowest-cost supplier. “Awarding a drug tender to a single supplier puts it at a high risk of shortage”, explains Badia-Tahull.

As API manufacturing has moved to emerging economies, such as India and China, this has created issues for meeting local and international demand and quality standards. With profit margins that are so narrow, companies producing raw materials have little incentive to invest in quality control or the resilience of their operations.

“Generic competition is fierce and profits are zero, so there is no financial incentive for them to invest in any kind of redundancy or resiliency,” says Fiona Scott Morton, Theodore Nierenberg Professor of Economics at Yale University School of Management. “If they could, that would raise their costs.”

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Razor-thin margins have led to poor quality control

The conflict between making medicines more affordable and providing sufficient price incentives for off-patent producers is also a prominent issue in Europe, according to Brian Godman a professor at the Strathclyde Institute of Pharmacy and Biomedical Sciences in Scotland.

“Across Europe, countries that want universal healthcare then want their medicines priced as low as possible,” he says. “As you

drive prices down, so you have issues with profitability. We have seen in the cancer field, as more new cancer medicines are launched and more of the older ones are seen as unprofitable by the originator company, then they have been sold to other companies.”

Sometimes, this process leads to further consolidation and puts producers in an especially powerful position. Professor Godman cites the example of Aspen, a South African generic pharmaceuticals holding company that has relaunched older products, often at higher prices, and was fined in Italy in 2016 for price gauging.⁷ These trends can be exacerbated if particular molecules are more complicated to produce and lead to smaller volumes.

“The resilience of the supply chain is not something that firms benefit from themselves, and so there is no incentive for them to address it,” says Mark Rosenberg, CEO of justmedicine.org, a U.S. non-profit that seeks to increase competition, quality and reliability of supply in the generics market. Ultimately, he says, generic producers suffer because they are seen as undifferentiated.

Are regulatory agencies fit for purpose?

At the same time, some of those interviewed for this paper believe that regulatory agencies, in their current form, are not themselves fit for purpose when it comes to evaluating the capabilities of foreign manufacturers.

In the U.S. the FDA has come under criticism for insufficient inspection of foreign API suppliers. They are accused of not requiring complete supply chain information about drugs sold in the US, including their purity levels. The FDA is frequently the only foreign agency with access to manufacturing plants*, but often lacks the

* Specifically, the FDA is the only body with access only if the manufacturing plant sells just to the US. But the FDA has Mutual Recognition Agreements with EU regulators, so the FDA will often be the only body to investigate even if they aren't technically the only ones who could.

understanding of industry methodologies and processes to do an appropriate evaluation, according to Mr. Rosenberg. Group purchasing organisations (GPOs), by contrast, have the expertise to be able to set up effective ratings of suppliers. There are few signs that this is happening on a regular basis, however.

“The reality is that we have not been terribly successful. It’s extremely challenging when you have GPOs saying they are doing rigorous vetting but no one other than the FDA are setting foot on the manufacturing site.”

Professor Scott Morton agrees, saying that “The FDA doesn’t even know where drugs come from. A lot of buyers and policymakers would like that information to be disclosed.”

One clear challenge to those trying to create a more robust system of evaluation of supply chains is the free rider problem, Mr. Rosenberg says.

“One of the major issues is that everyone benefits from a robust supply chain even if only one company is paying for it,” he observes, adding that health systems that purchase from higher quality suppliers should be first in line for their products.

CASE STUDY 1: Vincristine. Narrow profit margins lead to chronic shortages

Vincristine sulfate is used to treat adults and children with acute leukaemia and is sometimes used to treat some other types of cancer including Hodgkin’s lymphoma, neuroblastoma, and Non-Hodgkin’s lymphoma.

Nine of the 11 drugs for acute lymphoblastic leukaemia (ALL) were in and out of shortage between 2009 and 2019 with a huge impact on patient care.⁴ Some of these medicines are older, and less profitable, meaning purchasers rely on generic manufacturers to produce them. Manufacturers, meanwhile, are dependent on a limited supply of compounds derived from the *Catharanthus roseus* plant, commonly known as Madagascar periwinkle.⁸ One of these medicines is vincristine, shortages of which have significant impact on paediatric cancer patients.⁹

Problems with supplies of the cancer medicine were discussed at the Senate hearing for the new FDA commission in November 2020. An FDA commission nominee noted that vincristine is a critical chemotherapy drug that “has been included in nearly every treatment protocol for childhood cancer, as well as some adult cancers, for the past five decades.”^{10,11}

The cause for this shortage event was that one of only two manufacturers that supplied the US market had decided to discontinue the production of vincristine. Even though the FDA was involved in finding a solution to this crisis, resolving the production at a US manufacturing site was expected to take quite a few months.¹¹ A 2020 news report described the interplay of economic drivers and manufacturing problems as the main cause for the vincristine shortage.

Previous EIU research has also identified vincristine as one of several generic medicines that is repeatedly in short supply. A 2019 study of cancer medicine shortages in Germany found that vincristine and etoposide, two medicines dependent on naturally occurring active substances, were vulnerable to shortages.¹²

We revisit at the end of the report how our principles for improving supply chain resilience could have avoided or mitigated the shortages described in our case studies.

There is a lack of transparency along the supply chain

While it is clear that the supply of APIs is a consolidated industry, it is difficult to know exactly quite how consolidated it is. In a June 2021 paper, the French Academy of Pharmacy (Académie nationale de pharmacie or ANP) noted that the lack of a database recording which companies produce essential APIs, the ingredients that they use and the amounts they make, led to the realisation that nine out of 10 oral corticosteroid manufacturers were subcontracting to a single raw material manufacturer.¹³

In Europe, the European Medicine Agency's (EMA) Good Manufacturing Practice (GMP) procedures, implemented in 2013, were designed to improve API supply chain traceability.

The authors went on to say that regulations on pharmaceutical equivalence—defined as the same amount of the same active substance¹⁴—can be more complicated to meet when medicines are not registered centrally. Hurdles can also ensue when two different medications have the same active substance but cannot be administratively interchanged without making regulatory changes.¹⁴ Such situations can contribute to disruption of supplies.

Mr. Rosenberg agrees that the use of middlemen to secure supplies of raw materials raises transparency challenges. “We were looking at a healthcare system that was purchasing from three different pharmaceutical companies, and when you look under the hood, all three were using the same raw material supplier.”

In Europe, the European Medicine Agency's (EMA) Good Manufacturing Practice (GMP) procedures, implemented in 2013, were designed to improve API supply chain traceability. Yet some believe that the GMP might have inadvertently caused some shortages.¹⁵ It is suggested that the regulations established by the GMP might have hindered the flexibility purchasers need to adapt to crisis situations or allow for transfers and other technical adjustments.¹³

Dr Badia-Tahull is similarly concerned. “Some of the regulatory issues don't contribute to the solution,” she explains. “Inflexibility in regulatory processes or standards for the entry of new manufacturers can delay matters. While you may be able to wait 6 months to have a new car, with some drugs a similar delay is devastating.”



CASE STUDY 2: Piperacillin-tazobactam. Too few manufacturers leading to fragility

Antimicrobials are a class of medicines that are frequently in short supply.² Shortages often occur on a global scale with significant impact on patient care. They also have an impact on stewardship programmes, thus potentially exacerbating antimicrobial resistance¹⁶ and leading to the use of less effective alternatives.

When a 2017 global shortage of piperacillin-tazobactam, a drug often used to treat sepsis, led many hospitals to switch to alternative antibiotics, at least one study found that rates of hospital-onset *Clostridium difficile* infection increased among adult patients.¹⁷

The main risk factor for antimicrobial shortages is the limited number of manufacturers. Driven by economic causes, the “antimicrobial drug and vaccine market has been abandoned by many pharmaceutical companies”.¹⁷ This is especially true for older drugs.

According to a 2018 WHO meeting report, available data for 10 antibiotics, including piperacillin-tazobactam, suggest that two API producers are involved in over 50% of the market authorisations (MAs) and that API sources in Asia are linked to 52% of MAs while European sources are linked to 47%.¹⁶ As a result a problem with one API manufacturer can lead to shortages lasting months or even years.¹⁸

This is exactly what happened in 2017 when an industrial accident at a Chinese factory led to a prolonged and global shortage of the medicine. The WHO report noted that whereas producers of antibiotics previously depended on European API manufacturers, most manufacturing of raw materials has now switched to China and India. The report emphasised the lack of transparency about the production of raw materials, observing that because this information is considered to be confidential and proprietary, it is generally the preserve of regional and national regulatory agencies where pharmaceutical producers seek market authorisation. This lack of transparency, the report concluded, “makes it difficult to perform a true risk assessment to determine areas of greatest vulnerability.”¹⁶

We revisit at the end of the report how our principles for improving supply chain resilience could have avoided or mitigated the shortages described in our case studies.

A vulnerability to external shocks

Sudden increase in demand for specific products, or sudden events that affect API manufacturers, can lead to shortages, especially when the number of manufacturers is small. One recent example has been the Bacillus Calmette Guerin (BCG) vaccine, which is well known as a tuberculosis (TB) vaccine. It is also used as a standard treatment option for non-muscle invasive bladder cancer, for which there is no therapeutic alternative. Increasing demand for the BCG vaccine globally, due to its purported use for covid-19, led to a shortage in 2020.¹⁹

Natural disasters can also create bottlenecks, especially when manufacturing of raw

materials is concentrated in a particular geographic area. In 2018, Hurricane Maria caused significant damage to Puerto Rico, where many saline bags for hospital use were produced, causing shortages.

According to some estimates, about 50% of medicines currently in clinical use include natural products.⁸ APIs derived from natural sources may be vulnerable to animal diseases or plant habitat reductions or restrictions (e.g., in the case of protected plant species). There is also the danger of impure batches of raw materials that require their destruction. This is an increasing problem given the lack of transparency in supply chains and the absence of incentives to invest in quality control.





CASE STUDY 3: Heparinoids. A combination of swine fever and over-consolidation

Heparinoids are used for treatment of pulmonary embolism, unstable angina, acute peripheral arterial occlusion, and deep vein thrombosis.²⁰ Unfractionated heparin is critical for a range of surgical and interventional procedures, including haemodialysis, for which there are few alternatives.

While alternative anticoagulants can be used for certain indications—for example, the newer oral anticoagulant drugs can be used to replace heparins for the long-term management of thrombotic and cardiovascular disorders—they cannot be used for some surgical and interventional procedures.

Global demand for heparinoids has continued to grow in recent decades, amid forecasts that the market for the drug could expand at a CAGR of 6.2-7.6% from 2018 to 2025.²¹

Yet, there are a number of factors that have put pressures on heparin supplies. Around 80% of the API for the medicine is manufactured by Chinese pharmaceutical companies.²² In 2008, Chinese supplies of heparin contaminated with over-sulfated chondroitin sulfate were linked to deaths of dialysis patients in the US.²²

“The main factors that have contributed to the problems in the heparin supply chain are derived from their origin, porcine mucosa,” says Dr. Luis Palomares, a pulmonologist at the Institute of Biomedicine and University Hospital Virgen del Rocio in Seville, Spain. “Any problem related to the extraction of the porcine mucosa can trigger difficulties in the supply. A very important percentage of porcine mucosa worldwide comes from China.”

Indeed, outbreaks of African Swine Fever (ASF), a highly contagious and fatal disease of pigs, have been reported in a number of Chinese provinces since August 2018 and in the EU5. The disease has spread, resulting in euthanasia of 30%-40% of the pig population. In September, Haiti recorded its first outbreak of the virus in 37 years, spurring fears that it might spread to the U.S., which has never had the disease.²³

In 2019 a German heparin manufacturer started to ration shipments to the US as a preventive measure.^{24,25} More recently, the covid-19 pandemic shut down abattoirs, resulting in a decrease in the availability of mucosa. The resulting scarcity has put upward pressure on the API price, leading to supply distortions in low-price countries.

What is the solution? Researchers argue that it is not only rational to address the fragility of a global supply chain relying on a single-animal raw material from a single country, but it is also feasible due to the availability of bovine mucosa in many countries in different world regions.²² Governments could also make temporary adjustments to procurement conditions, if the supply of heparin is being challenged by external factors or market conditions. The final, less attractive approach, is mitigation. For example, taking a more conservative approach to using heparin where it is strictly necessary, drug rationing and therapeutic substitution—where possible.

We revisit at the end of the report how our principles for improving supply chain resilience could have avoided or mitigated the shortages described in our case studies.

Covid-19 has revealed the fragility of the global system

The pandemic highlighted the dangers of a lack of geographic distribution of API manufacturers, as China and India locked down for weeks at a time, freezing production lines. The effects were felt across the world. In early 2020 the European Association of Hospital Pharmacists warned that actions were urgently needed to reduce the impact of the covid-19 outbreak on the availability of active pharmaceutical ingredients (API) and medicines.² While in Canada, intensive care wards—struggling with an influx of extremely ill patients—experienced shortages of sedatives and paralytics commonly used in the ICUs, according to Dr. Lisa Burry, a clinical pharmacy specialist at Mount Sinai Hospital and the University of Toronto.

The pandemic highlighted the dangers of a lack of geographic distribution of API manufacturers, as China and India locked down for weeks at a time, freezing production lines. The effects were felt across the world.

“We were using 12 to 15 times the normal volume of these drugs and for a much larger quantity per patient,” she says. “Most of the compounding ingredients are coming from two countries. With the surge in covid-19, we ran out, and the manufacturer couldn’t make more, so we were trying to source it from other countries.” And although Health Canada identified an alternative source in Switzerland, it made the drug with a concentration of 2%, whereas Canadian equipment was set for 1% concentrations, therefore requiring careful reprogramming of hospital equipment.

The pandemic did focus minds, though. During lockdown, manufacturers managed to provide the FDA with earlier notification of supply disruption than in the past, giving it more time to work with stakeholders to identify ways to maintain treatment and prevent shortages. Overall, 199 drug shortages were prevented in 2020, and just 43 new shortages occurred, compared to a peak of 251 new shortages in 2011.²⁶

The Coronavirus Aid, Relief, and Economic Security Act (CARES Act) expanded the requirement for manufacturers of certain drugs to provide information on permanent discontinuances and interruptions in manufacturing that could lead to shortages. It further set out a number of other measures, including a requirement that manufacturers of certain medicines and APIs develop, maintain and implement a redundancy risk management plan. Finally, it also required drug makers to report annually on the amount of each drug that they have “manufactured, prepared, propagated, compounded or processed for commercial distribution.”²⁶ Similar approaches were proposed in the EU in the European Commission Guidelines on the “Optimal and Rational Supply of Medicines to Avoid Shortages During the Covid-19 Outbreak”, published in April 2020.²⁷

Meanwhile, the justmedicine.org initiative has also sought to address what the organisation says is the FDA’s dependence on information volunteered by the industry itself and lack of consistent visits to manufacturing facilities or regular use of batch tests. For example, the FDA was forced to pull inspectors out of China in winter 2020 and is likely to have to spend a significant amount of time catching up on the backlog.²⁸

Chapter 3: Strategies for mitigation

A number of efforts have been made over the past decade to prevent or mitigate the results of raw material shortages, yet those interviewed say there are no easy solutions, a point of view shared by regulatory agencies such as the EMA.²⁹ We describe here how shortages may be addressed in a reactive (mitigating) or proactive (preventative) manner.²

Reactive (or mitigating) measures

Reactive measures address ongoing shortages and include, for example, expedited regulatory processes for approval of alternative treatments or different manufacturers, hospital contingency plans and guidance for clinicians facing a shortage situation (**Table 2**).

Table 2: Reactive or mitigating measures that can be taken to relieve the impact of drug shortages (with a focus on API shortages)

Measure	Description	Potential downside
Substitution	Choosing alternative medicines to replace those that are unavailable	Some medicines don't have an effective equivalent. Alternative medicines may cause health problems
Expedited regulatory processes	Allowing emergency authorisation of substitute medicines or approval of different manufacturers or production sites	Regulatory agencies cannot require companies to increase supply in response to growing demand
Short-term action to support the market	Strategic decisions by governments to ensure that they purchase sufficient supplies of an essential medicine, or discussions between regulatory agencies and manufacturers to resolve medicine shortages	This sort of arrangement can be complicated and is likely to be rare. The current structure of the market, with middlemen often dealing with far-flung suppliers could make this approach challenging
Rationing	Limiting or conserving medicines in short supply	Healthcare providers must decide which patients are in greatest need

Substitution and alternative sources of medicine

The two most immediate reactive approaches are rationing or looking for alternative sources of a medicine. Finding an alternative source is rarely straight forward. We saw in the previous section how the pandemic made it difficult for Health Canada to source propofol. When they finally were able to identify an alternative source, the medicine's supply came in at a different concentration, meaning teams had to adjust their ICU equipment. In the case of oncology medicine shortages, doctors are sometimes forced to use "third, or fourth-line medicines" or even postpone treatment in the worst case scenarios, according to Dr Burry.

The Canadian province of Ontario has a command group linking public hospitals, pharmacies, physicians and manufacturers, which had been involved in prediction modelling prior to the pandemic. The goal was to create a more resilient network with improved reactive capability. However, Dr Burry said the challenge of simultaneous global demand for the same products was unforeseen—the covid-19 pandemic was off the scale. "What we missed the ball on was calculating how much (of a medicine) you might need for a disaster, but not a disaster that would wipe out the supply chain for the entire world," she says.

“ What we missed the ball on was calculating how much (of a medicine) you might need for a disaster, but not a disaster that would wipe out the supply chain for the entire world. ”

Lisa Burry, Clinical Pharmacy Specialist,
Mount Sinai Hospital and the University of Toronto

Expedited regulatory processes

The EHP highlights the fact that medicines are unlike any other commercial product. They are an "essential component of patient care" and even just missing a dose may have significant clinical consequences for some patients.² But simply creating more supply of a drug during a shortage is not as simple as it sounds. Although buyers or government agencies can ask companies to increase production of drugs, they can't force private companies to do so. The FDA has repeatedly stated that it cannot require a pharmaceutical company to "make a drug, even if it is a medically necessary drug, make more of drug, or change how much and to whom the drug is being distributed."³⁰

However, during the covid-19 pandemic, the FDA has been able to amend regulations, allowing it to "prioritise and expedite" reviews of applications and inspections in order to mitigate shortages.²⁶ Such actions allow manufacturers—where there is a will and capacity to do so—to rapidly upscale production.

Short-term action to support suppliers and manufacturers

National agencies can act in a way that ensures the purchasing of a certain volume of medicine in order to incentivise manufacturers. For example, in 2019, Greece's National Medicines Agency said that in the case of heparin and immunoglobins, it intended to "commit to the required quantity of products in order to adequately meet the annual needs of the country." Such action can help address issues that may cause manufacturers to withdraw from the market—such as hospital tendering agreements that can lead to periodic changes in volume. It offers confidence to suppliers and manufacturers that it remains commercially viable to remain in a particular marketplace.

Similarly, authorities can directly negotiate with companies to try and convince them to remain in a market. Such negotiations will inevitably be confidential but can be influential. For example, in 2019, following manufacturing delays that had led to shortages of Vincristine, Israeli pharmaceutical company Teva had previously stopped producing the drug. Negotiations with the FDA followed. After offering to import the drug from other countries, Teva concluded that its best approach was to restart the manufacture of the medicine in the U.S.^{11,31} Although the details of the negotiations are not available, it seems likely that they played a part in Teva’s decision.

Rationing and hospital contingency plans

Rationing of medicines is often a last-ditch response to extended shortages of medicines.

The process of deciding how to allocate scarce drugs is fraught with ethical dilemmas.³² Even where decision-making frameworks are in place, rationing contributes to worse outcomes in patients forced to defer treatment.

Proactive (or preventative) measures

Preventive strategies focus on interventions such as early notifications from manufacturers, as required by US and EU legislation, and the establishment of national reporting systems that are regularly updated and available to different stakeholders and the public.[†] Another proactive measure is the creation of procurement practices that ensure there is more than one manufacturer for each product, so that the risk of a single supplier is avoided (**Table 3**).

Table 3: Proactive or preventative measures that can be taken to try and avoid drug shortages (with a focus on API shortages)

Measure	Description	Potential downside
Early notifications, assessing risk and forecasting demand	Ensuring that manufacturers notify purchasers of potential disruption. Collecting data from pharmacists and purchasers about expected demand	Lack of incentive for manufacturers working on tight margins
National reporting systems	Compiling data from manufacturers, pharmacists, clinicians and patients	Requires coordinated input from multiple stakeholders
Procurement practices	Greater transparency and coordination of procurement to ensure a diverse group of suppliers	Better oversight needed to determine how many manufacturers produce a given compound and ensure that production is not concentrated in a single geography
Alignment of incentives	Rewarding local and regional sourcing of APIs; greater geographical diversity or offering incentives to ensure that production isn’t excessively concentrated	Need to make onshoring of API production financially or commercially advantageous, which may involve subsidies from the public sector. Purchasers need to identify new criteria to assess producers—such as resilience and quality rather than focusing on those with the lowest cost.

* For more information on early notification, see (FDA) <https://www.fda.gov/drugs/drug-shortages/drug-shortages-non-compliance-notification-requirement>, and (EMA) https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-detection-notification-shortages-medicinal-products-marketing-authorisation-holders-mahs_en.pdf.

Early notifications, risk assessment and forecasting demand

Earlier intelligence about potential shortages can make planning easier. National authorities in five European countries—Denmark, Finland, Germany, Hungary and Italy—provide risk assessment for medicines affected by shortages, with Irish and UK authorities currently developing guidelines for managing medicine shortages that encompass risk assessments.^{33,34} Only eight countries globally (Australia, Belgium, Canada, the Czech Republic, Latvia, Portugal, Sweden and the US) require daily updating of drugs at risk of shortage, and two multi-country collaborations analyse the causes of shortages and offer measures to ensure patient safety.³⁵

Earlier intelligence about potential shortages can make planning easier. Only eight countries globally require daily updating of drugs at risk of shortage.

As noted above, insufficient supply and demand management predates covid-19. For example, at least one form of the antibiotic penicillin has faced ongoing shortages due to insufficient production.³⁶ In South Africa, inaccurate prediction of demand had become endemic, although the situation has recently improved, reports Professor Godman. “South Africa has improved its supply chain because it realised the forecasting was being devolved downward and not done very well,” he says. “So by putting in better IT to do better forecasting and better ordering, you can help reduce the shortages.” The country has also established a National Surveillance Centre

and early warning system for pharmaceutical supplies, which uses mobile applications and electronic systems to gather information.³⁷

Creation of national reporting systems

In the US, the FDA has been required to submit annual reports to Congress providing data about drug shortages under legislation passed in 2012.

The data is used to develop strategies for mitigation of existing shortages and prevention of future gaps.^{26,38} Since 2011 the number of reported shortages has been reduced from over 400 in 2011 to less than a 100 per year between 2013 and 2018.³⁰ In 2020 only 43 new shortages occurred.²⁶

In October 2021, the FDA announced the launch of a new NextGen Portal for reporting manufacturing volume data for drugs and biologics as part of the CARES Act. It claims the portal will “improve FDA’s visibility into the drug supply chain and will help the agency identify, prevent, and mitigate drug shortages.”³⁹

The issue of the fragility of API supply chains has become more prominent in the discussion about drug shortages in the last few years. A 2019 expert testimony report before the US Congress highlighted that it was simply not possible to conduct an accurate assessment of the security of the US drug supply due to the lack data about the volume of APIs from China or India, and what percentage of US drug consumption this represented. It was also impossible to establish the extent of the dependence on foreign sources of API, the resilience of the domestic production base, or the reliability of the facilities that make products for the US market.⁴⁰

Innovative procurement practices

Dr Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER) at the FDA, outlined to the US Congress in 2019 the importance of the location of API manufacturing facilities. Location matters—Dr Woodcock observed—not only in the context of medicine shortages, but also from a national health security point of view.⁴⁰

Government mandates could help create the right incentives to improve API supply chain resiliency. For example, the FDA or another agency could require final product manufacturers to ensure that they have at least two sources of raw materials that meet certain criteria in order to supply US public sector medical programs such as Medicare, Medicaid and the Veteran's Administration system.

Professor Scott Morton suggests “It would make them want to have redundancy,” while acknowledging that such a mandate would also be likely to raise prices, if only slightly. “There has not been a lot of effort to suggest this. People at the FDA and Department of Health and Human Services often do not think about market mechanisms as a first line of defence.”

The European Commission has similarly called on public purchasers to design innovative procurement procedures that take into account conditions other than price alone—conditions such as the resilience of the supply.



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Chapter 4: Geopolitics and reshoring

Shortages will always arise from time to time; no supply chain is perfect. But, as ever in medicine, prevention is better than cure. We turn now to longer-term solutions, with a focus on the particular difficulties faced by the EU, the role of geopolitics, and the arguments for and against reshoring.

The European Union. Waiting for a HERA?

In November 2020, the European Commission published a pharmaceutical strategy for Europe in which it proposed to establish a crisis management body, the Health Emergency preparedness and Response Authority (HERA), modelled after the U.S. Biomedical Advanced Research and Development Authority (BARDA). Although HERA is designed to focus on covid-19 vaccines, the June report by the French ANP argued that HERA, in conjunction with other EU institutions and member states, should also be responsible for coordinating and preventing shortages of essential medicines.¹³

Shortages will always arise from time to time; no supply chain is perfect. But, as ever in medicine, prevention is better than cure.

The ANP notes that conventional medicines that are already off-patent—such as anticancer drugs, antibiotics, corticosteroids and vaccines—are likely to be most at risk of shortage, along with injectable analgesics and sedatives.

Certainly, over the last few years the European Commission has focused on shortages. It has recognised the API issue, suggesting the need for “dialogue to explore relocation of API production in Europe”. However, European politics is complex. The EU has divided responsibilities between member states and the Commission so that the supranational body is charged with providing incentives to stimulate innovation, while member states retain responsibility for the older medicines that are most likely to be produced by generic manufacturers—and therefore most under threat of shortages. A briefing paper from the European Parliament²⁷ notes that EU legislation already exists (Directive 2001/83/EC), but that the European Commission (EC) cannot oblige companies to maintain product on the market—just like any regulatory agency. Member States instead have to transpose this directive into national law and enforce it themselves. Economic causes of shortages can therefore only be addressed by member states, as pricing is a national competence.

But is this the best arrangement? Dr Palomares thinks not, arguing that the EU needs to take a greater leadership role, including determining measures it can take on the supra national level to reduce the risk of supply difficulties. “The responsibility should fall on European Union, which should provide mechanisms to all member countries to avoid supply problems,” he says. “The delegation of responsibilities to the countries and regions increases the inequality of the member countries of the European Union [...] the European Union should consider encouraging the production and manufacture of products in European countries.” Dr Badia-Tahull agrees, explaining that regions and even nations are often too small to solve the problem, and that “it would be better if the EU could articulate a way to rapidly find solutions to shortages”.

The EC and the EMA, like other regulators, have established task forces to address medicines shortages and developed new reporting systems in the form of databases or registries collecting information on supply disruptions.

One of the reasons the US has been more successful in averting shortages after receiving notifications is that the FDA can negotiate directly with manufacturers. The EC and the EMA cannot do this, only the national regulators can.

What role for the regulators?

Regulators are beginning to take shortages seriously. The 2019 FDA report on root causes recommended several “enduring solutions” for shortages. These include gaining a better understanding of the impact of drug shortages on patients and the contracting practices that may contribute to shortages. The report also proposes the development of a rating system to incentivise drug manufacturers to invest in quality management systems for their facilities. Finally, it promotes sustainable private sector contracts to make sure there is a reliable supply of medically important drugs.⁴

The EC and the EMA, like other regulators, have established task forces to address medicines shortages and developed new reporting systems in the form of databases or registries collecting information on supply disruptions. The task forces aim to develop and coordinate actions to allow for the prevention, identification, management of and communication about shortages at the EU level (although many other actions, as described above, remain the prerogative of member states). “In Europe, it’s about getting better at identifying what are the high priority areas, particularly around antibiotics and anti-cancer and then working to say, what strategies we can put into place,” Professor Godman says. “Strategies should identify which areas need to be monitored most closely, and which therapeutic interchange programs need to be used if shortages arise.”

At a global level, the World Health Organisation (WHO) has also been mooting the possibility of prequalification schemes for biosimilars in an effort to enhance competition and reduce prices. “Say that across Africa you have 10 or 15 regulatory bodies and then you have the cost for the manufacturer to go to each of those 10 to 15 regulatory bodies?” says Professor Godman. “If you have a prequalification scheme being run by the WHO, then that should reduce the amount of work, really, involved in getting these medicines into the country.”

The rise of reshoring

During the covid-19 pandemic the “geopolitical dimension” of the issue of medicine shortages has become more apparent. According to recent estimates 80% of APIs for generic medicines and 40% of the finished products sold in Europe are from China or India. Even before the pandemic, the European Commission had recognized, with growing concern, the EU’s dependency on API manufacturers in China.²⁷

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Indeed, the ANP suggests that the EU should make it a priority to become less dependent on the global market. They propose the establishment of pharmaceutical independence through achieving a production capacity of 60% of the volume for all generic medicines (both raw materials and finished products) consumed in Europe, as well as ensuring that the remaining 40% is not produced in

a single geographical sector.¹³ This target would require, among other things, both a way of mapping the supply chains of generic and biosimilar medicines, the establishment of producers in Europe for molecules where they do not already exist, and the inclusion of generics in European-wide strategy, as well as at the member state level. Yet, this is likely to be a challenge, as there is little production of molecules derived from biotechnology in Europe. It would also likely require EU member states to reward or incentivise the meeting of such targets, which is likely to raise prices of drugs with very low margins, as Professor Scott Morton has suggested.

Covid-19-related shortages have also provoked discussions on establishing more production of API in the US.^{41,42} In February, the newly installed Biden Administration announced \$60 million in funding to support domestic API production and create a consortium to onshore essential medicine production.^{43,44} “What we learned from covid-19 is that when a pandemic occurs, whole regions may go into lockdown and whole flows of trade stop,” Professor Scott Morton says. “In the absence of being able to ensure that trade is going to go on, you might want to manufacture at home.”

Regardless of the difficulties involved, the lack of transparency about the volumes of API produced overseas, and the difficulty in establishing the extent of the dependence on foreign sources,^{43,44} makes the idea of reshoring look attractive. Reshoring (or repatriating) pharmaceutical manufacturing closer to the patient appears not only logical but also economically viable. It would likely also help patients and aide health security.²⁷



Reshoring to Europe has been on the agenda for some time. “Bringing back manufacturing to Europe is a measure that some of us been arguing for long before the outbreak of covid-19”, explains Dr Badia-Tahull. Indeed, there are movements afoot. In November 2020, the new Pharmaceutical Strategy for Europe was adopted.^{45, 46} It aims to create a “future proof regulatory framework” and to support industry “in promoting research and technologies that actually reach patients in order to fulfil their therapeutic needs while addressing market failures.” One of the four pillars of the strategy aims to enhance crisis preparedness and response mechanisms, create more diversified and secure supply chains, and address medicines shortages.^{45, 46}

There has been a similar realisation in South America about the dangers of overreliance on long supply chains. In Brazil, increased use of technology transfer in the manufacturing of biological and non-biological drugs could allow the country to become a regional supplier Professor Godman says. Other parts of the world are also moving toward regional production, Professor Godman says, citing recent discussions of collaboration between East African countries, as well as within the Southern African Development Community (SADC).

While the future remains uncertain, and the challenges considerable, one thing is for sure: reshoring is back on the agenda.

Chapter 5: Five principles for preventing shortages

Although drug shortages have been a bane for many years, the global pandemic has concentrated the minds of policymakers and health purchasers. There is an acknowledgement of the need to improve the sustainability of supply lines for essential medicines. It is clear that the current status quo is putting patients and purchasers in jeopardy of increasing supply disruptions.

Supply chains are increasingly global. In 2019, 72% of API manufacturing facilities that supply the US market were located overseas – 26% in the EU, 18% in India and 13 % in China.⁴⁰ From 2009 to 2019, the number of Chinese facilities producing APIs for the US market increased as a result of offshoring driven by the industry's desire for cost savings and less stringent environmental regulations, as well as increasing price pressures.

Coupled to the creation of long and fragile supply chains is the fact that profit margins are slim. As such, API manufacturers are unlikely to take the initiative to resolve the problem: they simply are not incentivised to invest in quality. “Generics are making zero profit, so who is hurt? The consumer,” says Professor Scott Morton. “Either they can’t get the drug or they are buying a \$200 replacement.”

Much has been written over the years about the problems of drug shortages, but perhaps the covid-19 pandemic has finally offered an opportunity for action. Improving resiliency will not be easy, but stakeholders in medicine supply chains can take some reassurance that theirs is not the only industry that is re-thinking the best way to do things post-covid.

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Looking ahead: five principles for preventing shortages

We suggest here five principles around which an improved system can be built. Specifics of implementation will depend on local national and supra national relationships, depending on geography. We have mostly spoken about Europe and the US in this report, but the challenges faced are global.

1. Aligning incentives

Tying together all the challenges described in this report is the fact that most actors in API supply chains have little or no incentive to improve the current situation. When implementing new processes, ensuring aligned incentives will be key to successful outcomes. For example:

- **API suppliers** need to have incentives to invest in both quality assurance and reliability. This also means finding ways to limit the focus purely on cost cutting. Avoiding this race to the bottom, and the industry consolidation that exacerbates it, is likely to require cooperation across borders as well.
- **Purchasers** need to invest ways of co-operating and setting criteria standards to improve quality. Better communication between purchasers and the willingness to work together to establish a new framework for tendering could help to avoid cut-throat competition for scarce essential medicines.
- **Governments** need to play a role too; in some cases new regulations will be needed, while in others, greater flexibility to allow for the substitution of suppliers.

2. Improved transparency and dialogue between manufacturers and purchasers

Much greater transparency is needed to identify the number of API producers there are for the raw materials that make up key drugs, and where they are located. Encouraging purchasers—whether they are hospital pharmacies or government bodies buying for larger healthcare systems—to spend more time analysing supplies and requirements will make it easier to forecast demand. The current situation, where buyers themselves often don't know from where they're actually sourcing material, does not allow market forces to operate. To do this effectively, there has to be much greater dialogue between purchasers, manufacturers and suppliers.

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This may be an area where the private sector can add some dynamism to the hunt for improved transparency. Some companies, such as Wizmed,⁴⁷ have looked to shed some light on API supply networks using database research engines that can provide information on shortages. This may also be an opportunity for Blockchain-based systems. These could provide a transparent and tamper-proof record of transactions.

3. Better preparedness

Improved transparency will allow buyers to be better prepared for possible shortages. There are proposals afoot in a range of countries to extend existing risk assessment initiatives, including horizon scanning. Such measures would help identify medicines that are likely to be discontinued due to withdrawal or changes in pricing, something that has already been successfully piloted in Sweden, an exemplar for other countries.⁴⁸

The use of predictive analytics to forecast demand is important for budgeting and logistics planning. Coupled with transparency and cooperation between national authorities on matters such as stockpiling, and with manufacturers and other supply chain actors, more accurate forecasting would help to prevent shortages.⁴⁹

4. Multiple providers

Market issues—in particular the concentration of the industry—are viewed as the cause of many shortages. In many cases, the industry is over-consolidated, with just one or two global providers for some medicines.

Although the World Health Organization (WHO) recommends a supplier base of at least three different manufacturers to prevent shortages from happening, this advice is frequently ignored. In an effort to save money, a generic firm might cut two supply chains down to one, and might have no problems, until that firm suffers an outage.

There needs to be financial and regulatory incentives for encouraging more entrants into the generics market. “Public leadership in the development of repurposed generics transforms the availability of competing manufacturers from a problem, due to the disincentive for private investment, into an opportunity, where production will be inexpensive after research is complete”, suggests the Institute for Health System Innovation & Policy.⁵⁰



5. Shortening the chain

More countries and regions are looking to move production of some essential APIs back onshore. Even before covid-19, recurring drug shortages and quality issues related to offshoring had encouraged commercial customers to de-risk their supply chains by including domestic manufacturers.

Reshoring is a complex issue. Certainly, in a globalised economy, it makes sense that producers should ensure that their suppliers are geographically diverse, and that all points on the supply chain communicate closely. As an extra layer of security, governments may wish to offer incentives and oversight to help companies re-shore some manufacturing to create strategic lines of production.

Revisiting the case studies

Following these principles would have helped prevent or mitigate the shortages seen in our case studies of vincristine, piperacillin-tazobactam and heparin (Table 4). There is no silver bullet, but better dialogue, greater diversity of supply and improved incentives will go a long way to building more a resilient supply of APIs, and finished products. Much to the relief of pharmacists, doctors and, most importantly, patients.

Table 4: How our case study shortages might have been avoided, or mitigated, had one or more of the above policy principles been in place

Case study	Benefits of the five principles
Vincristine	The low profitability of vincristine, an older medicine, and producers' dependence on a natural compound that is in short supply are the key challenges in producing the drug. Better alignment of incentives could encourage manufacturers, while improved dialogue between producers and purchasers might at least provide warnings when production is likely to be disrupted.
Piperacillin-tazobactam	The problems involved in producing the antibiotic are largely due to the small number of producers of its raw materials, raising the risk that manufacturing problems will lead to shortages. Ensuring that there are multiple suppliers of the APIs for the medicine would go a long way to solving the problem; shortening the supply chain might mean earlier warnings when problems occur. Both of these solutions are likely to require creative incentives for manufacturers.
Heparin	Of the three case studies listed here, heparin is arguably the medicine most vulnerable to external shocks. Better preparedness for shortages and shorter supply chains—with more geographical diversity and higher sensitivity to API price distortions—would help avoid the worst disruption. In the meantime, regulatory flexibility can help ensure the marketplace can continue to operate.

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