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# Medicines shortages

## Global approaches to addressing shortages of essential medicines in health systems

**Shortages of essential drugs are becoming increasingly frequent globally, burdening health systems with additional costs and posing risks to the health of patients who fail to receive the medicines they need.**

**The problem has received increasing attention in recent years. Building on the outcomes of previous discussions, participants at a WHO-convened technical consultation reviewed the factors contributing to medicines shortages and discussed approaches that could be effective to prevent and manage them at the global scale.**

### Background

Shortages of essential medicines have been reported from high-, middle- and low-income countries. They are expensive for health systems to manage, causing additional costs for replacement of medicines and absorbing significant staff time (*Box 1*). Medicines shortages pose risks for patient health as a result of non-treatment, under-treatment and possible medication errors from attempts to substitute missing medicines.

While medicines shortages are not a new phenomenon, they have been increasing in recent years (*1, 2*), prompting international concern about long-term supply of key medicines.

A technical consultation was hosted by WHO in December 2015 to discuss the bottlenecks and reasons for shortages, consider existing solutions and identify approaches that could be effective at the

global scale (*3*). The discussions built on the findings and recommendations of an earlier summit meeting convened by International Pharmaceutical Federation (FIP) in 2013 (*4*).

### Types of medicines affected

Available data indicate that products in short supply include many commonly used medicines such as antibiotics, cancer medicines, cardiovascular medicines and anaesthetics. Many of them are off-patent products and are difficult to formulate or have a tightly defined shelf life. This combines with characteristics at the levels of manufacturers, buyers and supply chains as described below.

As a first step in defining a global list of essential medicines at risk of shortages a preliminary analysis was presented at the meeting, comparing the WHO Essential Medicines List (EML) with four

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current public databases of medicines in short supply. Adrenaline (epinephrine) and atropine sulfate were listed in all the databases reviewed, and many antibiotics – especially the cephalosporins – were listed in three out of the four databases. A well-studied example of an affected antibiotic is benzathine penicillin, which has been in chronic short supply for several years with global implications (5). Another example is insulin, which can be accessed reliably by only half of the 100 million people around the world who need it (6). Children's medicines are also often affected by shortages, representing a separate and important issue.

### Factors contributing to shortages

A range of causes and contributing factors combine to create situations where the demand for a medicine is not met by adequate supply.

#### *Demand side*

Unexpected demand changes or fluctuations can lead to medicines shortages, and the risk increases with the use of just-in-time inventory control where facilities sometime hold no or insufficient buffer stock. Uncertain availability can in turn lead to "hoarding" and to informal

exchange of stock through the grey market, posing risks for drug quality.

With increasing international funding for treatment of priority diseases there has been an increased demand for certain medicines in low- and middle-income countries that have not historically been large buyers in the global markets. Significant demand changes can occur in this global marketplace, for example due to changing treatment guidelines. In case of a shortage, local attempts at solutions sometimes merely transfer a shortage from one country to another.

A host of factors challenge the successful procurement of medicines from global markets. Commonly reported problems include fragmented demand, rigid rules on tenders, rigid shelf life requirements, overly customized specifications and payment issues. All this can lead to manufacturers refusing to participate in tenders, or holding orders until they combine to full batch quantities to be able to supply from fresh production.

At the supply chain level, unreliable data from peripheral facilities continue to be a major problem in most low- and middle income countries, hindering coordinated stock management and effective forecasting.

#### **Box 1: Medicines shortages: a widespread and persistent problem**

- In the U.S., new drug shortages rose from **70** in 2006 to a high of **267** in 2011. The total number of new and ongoing shortages crossed the 450 mark in 2012 (1). In an example cited by FIP, shortages cost U.S. hospitals US\$ **416 million**, i.e. US\$ 200 million to purchase more expensive alternatives and US\$216 million in labour costs .
- In a large European survey, **21%** of hospital pharmacists reported experiencing a shortage of medicines every day, a further **45%** every week. One in five pharmacists felt that they could not manage the shortage all or most of the time, suggesting that medicines shortages cause patients to suffer disruption to their treatment. (2)
- Fewer data are available from low- and middle-income countries. However, the experiences reported at the meeting by national and international actors suggest that there are significant challenges in ensuring access to needed medicines.

Payment systems can cause problems in both high-income and low-income countries. Limited health budgets are creating downward pressure on prices, threatening manufacturers' ability to maintain quality manufacturing. However, sudden changes in payment structures or perverse incentives to use expensive products seem to cause as much trouble as not having sufficient funds.

### *Supply side*

For a viable market model, a supplier base of at least three different manufacturers is generally considered desirable. For some needed products, particularly those which are less attractive from a marketing perspective, the manufacturing base is very limited. Mergers and acquisitions have further reduced the number of manufacturers that produce certain finished products. For instance, in the U.S., the majority of the injectable generic products is supplied by only seven major manufacturers (4).

Medicines shortages have been increasingly related to quality and raw material problems at the manufacturing level. In the globalized pharmaceutical markets there is an increased competition for active pharmaceutical ingredients (API). There has been a move towards API suppliers from emerging economies, such as India and China, which have come to experience tensions in catering for local and international demands and quality standards. Yet these sources cover a significant part of global API needs and are not easy to replace at short notice.

Maintaining quality systems for finished pharmaceutical products in line with current, international standards has become a complex and expensive endeavour. Moreover, long timelines to regulatory approval and diverse

or frequently changing regulatory requirements make market entry in many target countries costly and unpredictable. These challenges contribute to quality-assured finished products of certain essential medicines being scarce on the global pharmaceutical market.

### **Meeting recommendations**

#### *Risk-based public health approach*

Noting that shortages of medicines directly impact the health of patients, the meeting participants emphasized that a patient-centred approach to managing medicines shortages is required. Risk management principles should be used to identify and prioritize measures to ensure the continued supply of the medicines that are most needed in public health systems.

#### *Effective stakeholder discussion*

Coordination, communication and transparency should be fundamental principles in all actions between stakeholders at the national, regional and global level. Civil society and professional associations should continue to play a role in preventing and managing global stock outs. With their position in communities and other forums, they frequently have access to information that would be useful in detecting, or responding to, medicines shortages.

#### *Procurement*

Understanding global and national demand, especially for vulnerable products, was recognized as important. The experience of market shaping by global organizations could be leveraged. It should be noted that existing strategies have often been developed for medicines with single indications managed under specialized treatment programmes – such

as vaccines or antiretrovirals – and would likely fail for many of the medicines that have indications across several categories of general medicine.

Tender and procurement practices should be critically reviewed to identify possible causes of shortages. While there may not be a single perfect solution, it was recognized as necessary to consider the nature of each product, the available alternatives on the market as well as market demand in establishing tender conditions. Approaches that have improved the availability of certain medicines in pooled procurement mechanisms could be considered, such as advanced purchase commitments for priority drugs, engagement of manufacturers, credit facilities that promote consistency and predictability of cash flows, and consolidation of product specifications.

#### *Supply chain management*

Participants agreed that the importance of promoting efficient and effective management throughout the supply chain cannot be overemphasized.

IT systems that facilitate both upstream and downstream collection of information need additional support. Rapidly advancing the use of standardized bar coding – for example using GS1 as a common standard – was acknowledged as important and feasible.

#### *Ethical medicines use*

Ethical approach to management of shortages were discussed using examples from specialist areas of medicine, such as paediatric oncology, and national experiences for example in Canada. Suggested principles include evidence-based clinical decisions, fair access to

medicines across different populations, including clinical trial patients, and across phases of treatment. It was also proposed that criteria should be defined to prioritize the use of medicines in short supply, noting that this may be controversial. Ideally, agreement on a management approaches should be reached before shortages occur.

#### *Pricing*

A fair medicines price must be viable for the supplier and affordable for the buyer.

Exceedingly high prices are making some patented medicines unaffordable for health systems, and measures to ensure affordability have been much discussed for example for antiretrovirals a decade ago, and more recently for cancer treatments and new medicines to treat tuberculosis and hepatitis C. Meeting participants felt that negotiation with the patent holder to reach a mutually acceptable agreement should be the first approach. If this fails, the flexibilities of the TRIPS agreement such as compulsory licencing can be used; however this has significant costs and implications and should be carefully considered.

At the other end of the spectrum, the low prices of certain off-patent medicines are contributing to medicines shortages. For example, methotrexate is crucial to the treatment of many oncological and immunological conditions, yet it has been reported as in short supply repeatedly. Would an agreed global minimum price help keep it on the market? How would such a price be set? Meeting participants agreed that more transparency about the cost of production and the basis for pricing would be helpful to enable a constructive dialogue between manufacturers and procurement groups.

### *Regulation*

Drug regulators themselves have limited scope for action, since while they can keep a drug off the market, they cannot require a company to make a product. Approaches to prevent and mitigate supply interruptions, such as mandatory notification by manufacturers of current or impending shortages, and expedited inspections and reviews to incentivize manufacturing of good quality needed products, have been adopted for example by the U.S. FDA (7).

The value of good practices in responding to shortages, and of understanding the interaction and impact of regulatory decisions on availability of medicines, was recognized. Regulatory best practices should be collected, where possible harmonized, and provided as guidance to others.

### *National reporting systems*

Notification systems of medicines shortages exist in most high-income countries but are not yet required in many low- and middle-income countries (LMIC). However, existing databases have different definitions and approaches. For example, a “shortage” may be reported when health facilities are unable to pay for medicines, which does not mean that the product is unavailable on the market. In some databases the reason of shortage is given as “unknown” for almost half of the reported stock-outs.

It was agreed that it would be essential to harmonize definitions of “stock outs” and “shortages”, noting that work has commenced on this in some groups, and to establish standards for reporting that can be used for databases generally. Harmonization of reporting systems according to best practice would facilitate collaboration between regulators and

would support countries without an existing mechanism in establishing one.

### *Global notification system*

A global reporting mechanism could provide valuable insight into the development of the global medicines market. Such a system could monitor a list of medicines yet to be prioritized based on product and market characteristics. Data contributed to a global reporting mechanism would need to be from verified sources and must be validated. The value of having public access to databases as well as public reporting was clearly recognized.

### **Way forward**

The following priorities for WHO were identified based on the meeting outcomes:

1. Develop a consolidated list of medicines that are in short supply and are critical for use in medicine (from the WHO essential medicines list) or are at risk of short supply.
2. Develop an approach to market shaping for these medicines in collaboration with global partners.
3. Facilitate harmonization of definitions used in relation to shortages.
4. Consider development of a global shortage notification system, resources permitting.
5. Facilitate development of global best practices for regulatory authorities in relation to notification and management of shortages, including data standards, database management and regulatory/legislative strategies to minimize impact of shortages.
6. Work with partners such as global industry representatives and professional associations to develop good practice standards in managing shortages.

7. Work with global partners to develop consolidated volume and consumption data for 'vulnerable' medicines.
8. Work with partners to develop appropriate pricing strategies to ensure supply of 'vulnerable' medicines.
9. Continue to support countries, with global partners, to improve supply chain management, including up to date guidance and policies.

The issue of drug shortages was brought to the attention of the WHO Executive Board in January 2016 (8) and will be discussed as a specific topic for the first time at the World Health Assembly in May 2016.

### Conclusions

Shortages of key medicines will likely continue to be a problem. Meeting participants recognized that shortages of medicines and technologies are of concern to all countries, and that a coordinated, end-to-end approach across the health system is needed to mitigate their impact on public health. Global institutional leadership will be required to move forward on priority issues for improving access to needed medicines in health systems.

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