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# **Addressing the global shortages of medicines, and the safety and accessibility of children's medication**

## **Report by the Secretariat**

1. In recent years, shortages of essential medicines have been documented in most parts of the world with increasing frequency. The common denominator for these shortages is that medicines likely to be in short supply are products that are mostly old, off-patent or difficult to formulate and that have a tightly-defined shelf life and few or a sole manufacturer.<sup>1</sup> Injectable products are particularly at risk. The reasons for shortages have been investigated in many studies and in several countries, and the leading possible causes include: difficulties in acquiring raw materials, manufacturing problems, barriers to competition, business decisions, the impact of new technologies, expensive medicines, and fragmented markets.
2. These reasons combine with characteristics of supply systems to worsen any interruption in manufacturing. Notably, there is poor availability and quality of data on actual demand; inadequate management practices in procurement and the supply chain, combined with large tender contracts that do not sufficiently define quality standards but whose sole emphasis is on obtaining the lowest prices; and too small profit margins for manufacturers – all these factors may lead to shortages. Benzathine penicillin, for example, has been in chronic short supply for several years because of problems with manufacturing and thus the quality of the product, lack of consistent demand, and a decrease in indications for its use and a relatively low price.<sup>2</sup>
3. Medicines for children are also subject to shortages. Many regulatory authorities have limited capacity to undertake appropriate regulation to ensure good-quality products for children, clinical trials are not always done in paediatric populations, and there are problems with the capacity to diagnose uncommon diseases in children. Examples are endocrine disorders in children, which can be treated very effectively – when they are recognized – with a small group of essential medicines that are mostly off-patent but seem to be in short supply globally.

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<sup>1</sup> Gehrett BK. A prescription for drug shortages. *Journal of the American Medical Association* 2012;307:153–154. doi:10.1001/jama.2011.2000.

<sup>2</sup> Wyber R, Taubert K, Marko S, Kaplan EL. Benzathine penicillin G for the management of RHD: concerns about quality and access, and opportunities for intervention and improvement. *Global Heart* 2013;8:227–234 DOI: <http://dx.doi.org/10.1016/j.gheart.2013.08.011> (accessed 7 December 2015).

## CONSEQUENCES OF SHORTAGES

4. Negative impacts of shortages are inability to fulfil prescriptions as well as poor quality prescribing and poor use of medicines. The results are poor health outcomes, which have been documented, for example, in relation to mortality in children owing to lack of cancer treatment and to inappropriate use of antibiotics when first-line regimens are not available. Inappropriate use of second- and third-line regimens can contribute to drug resistance, limit treatment options and often have higher cost. The global burden of undertreatment and failure to treat is not known; however, the problem of shortages, given their increasing trend, combined with poor use of medicines will become increasingly complex to resolve. Where shortages have been experienced, there have been reports of spurious/falsely labelled/falsified/counterfeit medical products entering the supply chain, with risks for the health of patients.

5. High-income, middle-income and low-income countries all may have different reasons for shortages in relation to supply chains, but payment systems for products can cause problems in all settings. Changes in payment structures or systems that provide perverse incentives to use expensive products may also lead to shortages of low-priced alternative treatments. Rigid, lengthy or inadequate tender processes may also contribute to the problem and, although there may be strategies to limit the risk of supply through sole tenders (for instance, penalties for failure to supply), research is needed on how effective these have been in reducing shortages in different settings.

## COUNTRY APPROACHES TO LIMIT SHORTAGES

6. Several strategies have been tried to avert or reduce shortages. Multiple reporting systems exist within specialized programmes or at national level in high-income countries. For example, manufacturers in European Union member states are obliged to inform the health authorities in advance of possible future shortages. A combination of notification systems and systematic regulatory and reimbursement responses may help at a health-system level, together with a systematic approach to the clinical use of products in short supply. It is not clear yet whether mandatory or voluntary notification works best and who should do the notifying – let alone considerations on whether these processes can be applied in countries with weak regulation and information systems.

7. Additional approaches to managing acute shortages, preventing future shortages and reducing the impact of shortages on the provision of care to patients include: the use of online information systems to facilitate direct reporting to health authorities of information on shortages; coordination between producers; and, in some situations, the use of exceptional procedures for the granting of market authorizations. Also, some countries have promoted initiatives to encourage the production and registration of generic versions of medicines in short supply.

8. Mechanisms for combining and sharing notifications for global scrutiny of the status of the supply of individual medicines could be investigated and explored. As the supply of pharmaceuticals is a multinational business, having a system for comprehensive evaluation and a future global monitoring mechanism for that supply in place, would anticipate and detect early shortages and assist the development of a joint rapid response mechanism to encourage countries, the international community and other relevant stakeholders to cooperate in developing a joint rapid response.

9. Pricing interventions can also be used to reduce shortages. In the Australian context, manufacturers can request a higher price for products with limited markets.<sup>1</sup> It has been suggested that in the context of the United States of America, where prices of oncology products decreased following the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, that setting minimum prices for some products in order to encourage continuity of supply would improve supply of oncology products.

10. It is important to develop proactive strategies with actions to be taken to identify and maintain the supply of medicines that are essential for health care and that are vulnerable to shortages in supply. The usual market approach to medicines supply through encouraging generic manufacturers to produce the medicines of interest has shown enormous benefits in lowering prices and increasing affordability. Too low prices, however, may drive manufacturers out of the market, and higher prices of alternative newer products may result in them being preferentially supplied, with a decline in market for vital but cheaper medicines. Limiting competition can also result in problems with supply.

## **NEW STRATEGIES TO MITIGATE THE RISK OF SHORTAGES**

11. At the global level, a set of essential medicines could be identified for which shortages have been reported or there exists a risk of shortages, and an international agreement about ensuring continuity of manufacturing and supply could be investigated. For example, successful treatment of many oncological and immunological conditions without methotrexate is severely jeopardized – yet this product has been reported as in short supply repeatedly. Questions that a general international agreement would have to resolve include: could a multi-year global advance purchase commitment be worked out? Would an agreed global minimum price that is commercially attractive help to keep a medicine on the market? How would such a price be set?

## **MEDICINES FOR CHILDREN**

12. The adoption by the Health Assembly in 2007 of resolution WHA60.20 on better medicines for children led the Secretariat to introduce a programme of work on that subject. Its results have included creation of the WHO Model List of Essential Medicines for Children (most recently updated in April 2015), the setting of global standards for formulations of medicines for children, identification of clinical trials in children through the WHO International Clinical Trials Registry Platform, publication of information about prices of selected medicines for children, and identification of missing products, such as fixed-dose combination medicines containing the appropriate dose of the components for tuberculosis in children.

13. The shortage of treatments of tuberculosis for children was successfully addressed by WHO and its partners. After a change in tuberculosis treatment guidelines in 2010, the pharmaceutical industry was reluctant to invest in redeveloping medicines to treat children with tuberculosis, citing the cost of new trials for regulatory submissions and the fact that the market was small and poorly understood as barriers to investing. UNITAID's STEP TB Project invested in trials to reduce risk and engaged with manufacturers to ensure regulatory submissions. The Project also worked with countries with high

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<sup>1</sup> See Australian Government Department of Health, The Pharmaceuticals Benefit Scheme, <http://www.pbs.gov.au/info/industry/pricing/pbs-items/fact-sheet-requesting-a-change-to-an-existing-price> (accessed 7 December 2015).

burdens of tuberculosis and major procurers to improve the ability to quantify the actual demand and need.

14. Shortages of each product (or group of similar products) will have different causes and their rectification will require specific and targeted interventions. Other products for children are also listed on the invitations for expression of interest issued by the WHO Prequalification Programme for HIV/AIDS, including hepatitis B and C, and malaria, and interventions continue with the aim of securing their availability, from manufacturing to national supply chains.

15. The Paediatric medicines Regulators Network was established to promote collaboration between regulatory authorities on the regulation of medicines for children. Some high-income countries have legislation related to medicines for children with the aim of optimizing and promoting the development of appropriate products, but similar legislation is not generally in place in low- and middle-income countries. There will be value in further developing the Network and providing more support to countries for building appropriate capacity to regulate medicines for children appropriately and encourage their research and development.

16. Prices of paediatric medicines are generally higher than equivalent products for adults. In part, this price differential may be due to higher development costs of special dosage forms for children and the need for additional clinical trials. A better understanding of research and development costs would enable a constructive dialogue on how to establish a fair and affordable price for medicines for children.

17. Understanding the costs of development of medicines is particularly important for uncommon and genetic diseases in children (variously classified as orphan and rare diseases). New and effective products for many genetic disorders are becoming available but they are generally extremely expensive. Further there is a degree of confusion between what are truly orphan or rare diseases, based on the global burden of disease, and what have been defined as orphan diseases for the purposes of regulatory authorities who can provide incentives for manufacturers to encourage their development and production. There is some evidence that these incentives are now being exploited, resulting in high prices and problems with access. Should a country choose to make these products available through health insurance schemes, the impact on their pharmaceutical budgets can be substantial.

18. Overall, the demand side of the market for many medicines may need to be more actively managed. There are limited data to guide manufacturing and procurement decisions about medicines for many diseases in children. At the same time, health care workers try to provide effective care through the use of extemporaneous preparations, which may offer short-term solutions but may also be

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