Executive Board, 138th Session, 2016
Agenda Item 10.5
Addressing the global shortages of medicines, and the safety and accessibility of chidren's medication.

Background

Stock-outs and shortages[1] of medicines, vaccines and diagnostics is a challenge that MSF frequently encounters in our operational settings. Shortages and stock-outs lead to treatment delays or interruptions, and put patients' health outcomes at risk. Shortages and stock-outs also have broader public health implications: for treatment of HIV and other infectious diseases, they can lead to viral and bacterial resistance. Furthermore, patients confronted with stock-outs may lose trust in the health system, while health care workers -- already challenged in difficult settings -- face additional workload and frustration.

MSF notes the challenge of development, production and access to some basic essential medicines[2], including paediatric medicines as specifically referred to in the Secretariat's Report, and provides some observations below.

Stock-outs and shortages have been poorly understood, and the Secretariat Report points to the fact that the 'global burden of under-treatment and failure to treat is not known'. Indeed, this is because access to medicines at the patient level is not routinely monitored or reported. MSF welcomes recognition of the fact that there is limited, incomplete and often inaccurate data of actual demand.

Broadly speaking, MSF notes the following drivers of stock-outs and shortages:

- Production difficulties
  - Quality problems
  - Good Manufacturing Practice (GMP) noncompliance
  - Lack of Active Pharmaceutical Ingredient (API) source
  - Long lead time to produce adequate quantities to meet needs
- Insufficient number of producers
  - Unattractive or inadequate market (with some pharmaceutical companies increasing their focus towards more lucrative products and markets, without a sustainability plan for other product lines)
  - Intellectual property barriers that restrict market access for multiple suppliers in one country or that restrict the number of suppliers worldwide
  - Commercial decision to discontinue manufacturing
- Lack of accurate forecasting
  - Strategies for treatment of HIV, for example, that will significantly stretch supply chains [3]
- Suspension of donor support / transitioning of donors from many low- and middle-income countries (wherein donors have played a critical role supporting procurement and supply)
- Inefficient tender policies and/or procurement processes

[1] Shortages are generally associated with production problems; stock-outs are generally associated with the unavailability of a medicine on the pharmacy shelf
[2] e.g. the global shortage of penicillin
[3] The current WHO HIV treatment strategy recommends treating all HIV patients, regardless of CD4 count. WHO has adopted a tiered care model to bring HIV care closer to patients while providing longer refill intervals. Regimens for HIV will continue to change with increased viral load testing and need for salvage treatments.

- Stock not disseminated through the supply chain, including last-mile delivery challenges
- Arbitrary price reductions imposed by governments without consideration of impact
- Delay in importation
- International sanctions experienced by some countries

To underscore the multitude of products (adult and paediatric) for which MSF has faced shortages, an Annex is included with this submission.

MSF Feedback on Secretariat Report

Scope of the Report

1. **The scope of medicines covered by the report is insufficient.** The report aims to define the scope as medicines 'not produced to an adequate extent' and 'mostly old, off-patent or difficult to formulate and that have a tightly-defined shelf life and few or a sole manufacturer'. While those product categories are relevant, there are other categories of medicines that must be included. For example, many critical HIV and TB medicines do not fall within the above definition. However, MSF experience has shown that shortages of these medicines happen acutely in countries during critical periods such as regimen changes or treatment scale-up (or increase in global demand). The report also does not take into account on-patent medicines, whose shortages can be caused by monopolies. Some vaccines, as well as certain rapid diagnostic tests (e.g. brucellosis) must also be considered.

2. **The impacts of such shortages extend beyond those documented in the report: a greater focus on impacts at the end user level is required**. When faced with stock-outs or shortages at health facilities, MSF has witnessed patients experiencing physical and mental stress, increased financial burden (transport costs, purchasing medicines from alternative sources) and a general loss of confidence in the health system. Furthermore, shortages can lead to healthcare workers spending extra time placing emergency orders, redistributing medicines from other facilities or trying to define appropriate alternative regimens. When such measures do not succeed, treatment interruptions and a higher risk of resistance can result; in the case of HIV, shortages and stock-outs can negatively impact treatment adherence and ultimately undermine reaching viral suppression. Facility-level stock-outs should be monitored, as well as the related health outcomes in patients who are affected by them.

Causes of Shortages and Stock-outs

1. **The Secretariat report focuses mostly on global shortages, but does not examine or propose approaches to address country-level supply chain issues including last-mile delivery challenges.** The majority of stock-outs happen due to supply chain challenges. Most countries do not continuously monitor stock-outs at the facility level, which is an important indicator of how a supply chain functions. Countries with irregular last-mile delivery such as Mozambique, DRC and South Africa experience more stock-outs. Indeed, MSF has witnessed ARVs stock-outs in these countries, even though ARV vertical supply chain systems usually function better than the regular systems for other medicines. Thus, supply chain challenges for essential medicines may be greater with respect to availability at the patient level.

2. **The report should acknowledge patent barriers restrict market access for multiple suppliers worldwide or suppliers for any particular country which can have an impact on national and international suppliers.** Patents create barriers to enabling multiple suppliers for medicines, whether to produce for global demand or for specific countries. In South Africa, for example, lopinavir/ritonavir (LPV/r) is currently supplied by only one company, Abbvie, which holds a patent on the medicine. In 2015, demand for LPV/r exceeded forecasted amounts in South Africa and for over six months, Abbvie was unable to supply adequate quantities, leaving many patients to return home without medicines. Shortages were also reported in other countries

using Abbvie's LPV/r. Generic suppliers registered locally in South Africa were unable to supply due to the patent, and thus had not manufactured sufficient stocks to support other countries facing LPV/r shortages. Global plans to ensure supply security for essential medicines should be established as part of a systemic response to shortages, which take into account patent barriers.

3. **The report does not focus adequately on the obligations of the pharmaceutical industry related to shortages and stock-outs.** While the report indicates that one driver of using new, expensive medicines (thereby leading to reduced use of older, more affordable medicines) is the payment system of governments, it neglects to recognize the measures used by pharmaceutical companies to influence prescribing with perverse financial incentives. These may include, among others, training programs used by companies in developing countries to influence use of certain products.

   Secondly, the report does not note that companies often fail to accurately and promptly report existing or anticipated stock-outs and shortages, as was the case with Abbvie with its branded version of LPV/r, thereby leading to stock-outs in multiple countries where Abbvie held a patent and where there was no possibility of use of generic alternatives.

   Thirdly, companies have discontinued production for a critical product, or only produce certain medicines on demand due to low anticipated value. This has included Sanofi's decision to terminate production of its anti-venom, and manufacturers of paromomycin that only produce it on demand, leading to shortages in endemic countries.

Consequences of Shortages and Stock-outs

The report states that shortages of medicines are likely to lead to increased proliferation and use of substandard, falsified and counterfeit products (SSFFC). The presence of substandard and falsified medicines is associated with the development and functionality of national regulatory authorities. Given that many countries experiencing shortages and stock-outs may also have under-developed national regulatory authorities, it may be that there is correlation (not causation) between these two situations, although this should be examined more carefully.

Monitoring and Responding to Shortages and Stock-outs

1. **Inclusion of a global early warning mechanism for stock-outs and shortages, paired with a rapid international security response.** In order for such a response to be successful, it will require coordination from actors at the global, regional, national, and end-user level during critical periods to avoid shortages. Monitoring the availability and global demands of medicines should not be narrowly defined but should extend, for example, to HIV and TB, as well as to other essential medicines, vaccines and diagnostics.

2. **Global reporting requires inclusion of global manufacturing issues.** In recent years, this has included failures of production for LPV/r by Abbvie, kanamycin shortages in 2011, and a clofazimine shortage in 2015. Greater accountability and reporting by industry is urgently needed to address shortages in a more effective manner.

3. **Country approaches to limit shortages fail to mention the critical role that patients, health care workers and communities (end users) can play in several countries in monitoring and reporting shortages.** Patients, health care workers and communities can provide the necessary 'last level' data on availability of medicines at health facility level (and/or as quality control to the existing national data monitoring system). A globalized notification system and response mechanism should therefore involve end-users, and should create adequate communication channels between end users and governments to develop better stock-out resolution mechanisms.

Monitoring established indictors at the end-user level should be routinely done to measure supply chain performance, including availability and stock-outs of essential medicines. Furthermore, robust data collection at the patient level can support forecasting and quantification, and provide early warning signals on stock-outs.

4. **Exceptional measures to address global shortages.** MSF agrees that when acute shortages occur, a range of exceptional measures should be taken at the national level to overcome such shortages. This may include fast-track (and mutual recognition of other countries') registration procedures and compulsory licensing.

5. **Increased prices to reduce shortages are an exceptionally limited approach that could be applied in specific circumstances only.** Pricing interventions may exceptionally be made for therapeutic interventions where total expected sales do not support minimum commercial investments by pharmaceutical companies. MSF has witnessed shortages in such circumstances, but emphasises that these examples are rare and such pricing interventions should be equally rare. Minimum prices, when used, should be accompanied by a transparent audit by an independent third party.

Medicines for Children

1. **MSF cautions on declaring 'success' with respect to access to specific children's medicines, including TB medicines.** While placing a particular product on the Essential Medicines List (for example a fixed dose combination for children) is a good first step, the actual momentum to develop such medicines was not possible until UNITAID started to pay for trials and other aspects of drug development.

2. **Regulatory incentives, and in particular asking 'smaller' stringent regulatory authorities (SRAs) to push for development of paediatric products, will not impact the paediatric market.** If companies such as Janssen have not and will not develop paediatric versions of new TB medicines when the US Food and Drug Administration already has a voluntary component asking for such product development, regulatory incentives from other SRAs are unlikely to be successful. MSF agrees other incentives to invest in research and development for paediatric medicines are needed, and recommends coordinated push funding and pull incentives, in lieu of regulatory incentives.

3. **MSF welcomes transparency around the costs of research and development for new paediatric products as a means to develop effective responses**. Efforts to improve transparency of R&D costs, starting with paediatric medicines, is critical both to design effective incentives to encourage development of such products, and to avoid charging governments, medical providers and patients the high prices which can deny access to effective new medicines for children.

<u>Systemic Approach to Prevent and Manage Shortages of Medicines: MSF Recommendations</u>

MSF welcomes measures that introduce a systemic approach to address medicine shortages and stock-outs, but calls for an increased range of approaches.

Understanding and documenting shortages and stock-outs

- Make it mandatory for pharmaceutical companies to immediately inform Ministries of Health (MOHs) about supply problems and their causes.
- Increase attention on addressing the national and localized supply chain challenges which cause the majority of stock-outs.
- Measure patient level demand vs availability of medicines with indicators to evaluate patient access and in-country supply chain performance. Patients and civil society can play an important role in

providing this information when the national system cannot provide it or as a parallel source of information. Common indicators can be defined and measured to evaluate:
    - patient-level access to essential medicines (and can be replicated for other health products and technologies, such as vaccines and diagnostics)
    - supply chain performance
    - programs, including with linking to patient outcomes (retention in care, adherence, resistance)
    - forecasting and demand levels, to help improve both national and global planning.

Preparedness and Avoidance of Shortages

Globally:

- Develop and maintain a database of critical medicines shortages, including proposed alternative sources of supply and / or alternative treatment regimens
- Develop a list of products at risk of regular shortages, explore the reasons behind their shortages, and propose long-term solutions from a regulatory and procurement perspective (incentives for API and Finished Pharmaceutical Product (FPP) manufacturers to develop those products, aggregating demand, pooled procurement, etc.)
- Coordinate global demand with global production to ensure multiple available suppliers can access relevant markets, including implementation of TRIPS flexibilities to increase generic competition
- In specific, limited circumstances, introduce a minimum price to maintain incentives for manufacturers to maintain supply, while ensuring such prices are backed by transparent audits of cost of production

Regionally / Nationally / Locally:

- Create regional and in-country mechanisms to plan and monitor regimen transitions and scale-up that are evaluated on the basis of patient level access indicators and treatment outcomes. This can include advice on appropriate alternatives if shortages or stock-outs occur.
- Improve national intellectual property laws, to include flexibilities related to compulsory licensing and parallel importation, to be able to take quick steps to help alleviate shortages
- Increase collaboration of procurement and supply chain management, including
    - planning and forecasting for new regimens and treatment guidelines
    - evaluating patient-focused supply chain approaches, including the ‘last mile’ delivery
- Ensure legal mechanisms are in place in tendering, to oblige suppliers to meet the agreed delivery quantities

Responding to Shortages

WHO:

- Establish national, regional and international fora to: (a) measure, analyze and share stock data for early warnings on shortages, and (b) coordinate ‘critical’ periods when risks of stock-outs are higher, such as with ARVs (regimen changes and scale-up) via extra security stocks and alerts.
- Maintain a centralized database of SRA-approved sites of API and FPP manufacturers for critical medicines other than the products currently covered by WHO Prequalification, which could help to accelerate the process of approval in cases of shortages
- Extend Prequalification to all products at risk of shortage, to allow for access to complete and independent information on alternative sources of products (or alternative treatment protocols)

Ministries of Health / National Governments:

- Provide and disseminate medical recommendations / therapeutic alternatives
- Implement an expedited review process to evaluate the cause of the shortage
- Implement plans to allow for access to alternatives in as short a timeframe as possible
- Use TRIPS flexibilities to accelerate generic entry of alternative suppliers

Annex: Examples (not exhaustive) of shortages recently experienced by, or known to, MSF

Disease	Medicine, Manufacturer	Date (if documented)	Reason (if known)
Malaria	ASAQ, Sanofi	2012	problems of API (artemisinin) supply
	artemether injection 80mg/mL, Sanofi	2013	impurity problem
	rectal artesunate, Acino		mono-source
	SPAQ, Guilin	2015	sulfadoxine API shortage
TB	Kanamycin	2010	Mono-source of API; production difficulties
	Clofazimine	2015	production problems
leishmaniasis	sodium stibogluconate (SSG) and paromomycin (PM)	2014	unpredictable increase of cases; only one supplier each for the SSG and PM APIs; sole suppliers for the FPPs as well
vaccines / immunoglobulins / anti-venoms	hepatitis B multidose vaccine		procurement concerns
	rotavirus vaccine		supply was reserved by Unicef
	hepatitis A vaccine, GSK		production problem in Belgium
	BCG vaccine, Stantens Serum	2015	batch release problem
	meningitis vaccine (other than the Men A conjugate)		
	cholera vaccine		
	yellow fever vaccine		
	Rabies		limited approved sources; vulnerability of supplies
	Tetanus		
	anti-venom immunoglobulin		
	Ig TT, Baxter		stopped production (now mono-source from CLS Behring)
	Ig anti-venom, Sanofi		stopped production

Other Essential Medicines

- penicillins: benzathine benzyl penicillin 1.2 and 2.4 MIU, PPF (well-known worldwide problem; problem with one of the few API sources)
- digoxin 0.25 mg tablet (raw material shortages)
- suxamethonium chloride 50mg/mL 2mL ampoule
- cloxacillin (beta-lactam shortages)
- ketamine injectable
- dexamethasone injectable
- phenobarbital 200mg/mL injectable
- aciclovir eye ointment
- doxorubicin liposomal (only one approved supplier)
- dinoprostone 1mg vaginal tablet

HIV and TB Medicines in Southern and Central Africa

Analysis by MSF and other actors in four countries showed that over a 3 month time period[i];

- 77% (Q1 2015) of 94 facilities in Kinshasa, DRC had an ARV stock-out. Although the ARVs or an alternative formulation were available in country, in 68% of cases patients left the clinic without medicines.
- 43% (Q2 2015), 0% (Q3 2015) of 14 facilities in Nsanje, Malawi had an ARV stock-out. All ARVs were available in country.

- 41% (Q1 2015), 41% (Q2 2015) of 17 facilities in Tete and Maputo City, Mozambique had an ARV stock-out. Only 1/12 reported ARVs was out of stock in country in Q1, in Q2 all ARVs were available in country.
- 21% (2013), 25% (2014), of 2139, 2454 facilities in South Africa has an ARV and/or TB stock-out. Only 9% was related to a national stock-out.
- In 2015, facilities in South Africa reported ARV and/or TB stock-outs, due in part to national stock-outs of LVP/r as discussed above.
- Poorly coordinated regimen changes at introduction of TDF/3TC/EFV following updated WHO guidelines have led to in national stock-outs of ARVs in Mozambique, South Africa and DRC.
- Increased second-line demand following scale-up of viral load monitoring has led to national stock-outs in South Africa, Lesotho, Mozambique and local stock-outs in Malawi.

[i]MSF (2015. Empty shelves. Come Back Tomorrow. ARV Stock-outs Undermine Efforts to Fight HIV.