Pandemic Preparedness for Regulators in Low- and Middle-Income Countries

Mitigating medical product shortages, preparing the public, and protecting patients during the COVID-19 pandemic and beyond

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The spread of coronavirus (COVID-19) has turned into a global pandemic with alarming speed, prompting many to have questions about the stability of global medical product supply chains. Many low- and middle-income countries may face greater risk of medical product shortages as a result of COVID-19, and the pandemic may also exacerbate the ongoing problem of substandard and falsified medicines.

This pandemic is a true test of the global drug supply chain, and it is urgent that all players involved take appropriate steps to protect the safety of patients. During the 2014 West Africa Ebola outbreak, a lack of medical supplies and personal protective equipment was reported to have led to an increased rate of infections and poor control of the epidemic.[1]

To mitigate immediate COVID-19-related shortages of medical products, protect patients, and avert future supply chain threats, regulatory authorities should first identify potential disruptions and then develop strategies and contingency plans for addressing them. Presented below are five sets of interventions that can help regulatory authorities respond to the COVID-19 pandemic and future public health emergencies.

Mitigate current shortages

1. **Use data to forecast shortages.** Conduct immediate analysis to compare recently imported products with historical utilization trends to predict imminent shortages. Identify alternate sources for medical products and consumables currently on shortage or most prone to shortages.

2. **Rely on medicines approvals obtained in other countries.** Utilize waivers and related instruments to facilitate the availability of critically needed products not yet approved in-country, which have undergone stringent regulatory approval in other countries.[2]

3. **Monitor quality of inactive ingredients.** To mitigate potential risks from the rise in use of analgesics, regulatory agencies should develop and share a list of local suppliers for inactive ingredients, or excipients. Many local pharmaceutical manufacturers source excipients from unregulated chemical dealers. Cheaper, toxic, industrial-grade ingredients often enter into the supply chain. In 2008, the use of diethylene glycol for the manufacture of *My Pikin* – acetaminophen syrup teething medication led to the death of 54 children in Nigeria. In order to maintain production during the COVID-19 crisis, local manufacturers might turn to new, unknown suppliers, which could compromise the product's safety and be harmful to patients.

4. **Compounding pharmacists can fill in gaps.** Compounding practices need to be reviewed and strengthened. Regulators should collaborate with Pharmacy Council and other pharmacy practice regulatory agencies to strengthen Good Compounding Practices.

5. **Lean on local medical equipment manufacturers.** Regulatory authorities should link hospitals with local manufacturers of personal protective equipment (PPE) such as gloves, masks and other medical devices such as respirators. To ensure continuous availability of hand sanitizers, several organizations including the U.S. Pharmacopeia Compounding Expert Committee, the World Health Organization, and the U.S. Food and Drug Administration have issued recommendations for preparing alcohol-based hand sanitizers.

Strengthen shortage surveillance systems

1. **Establish early warning systems to identify imminent shortages.** Develop guidance for detection and notification of shortages of medical products, and require manufacturers to disclose supply disruptions.[3]

2. **Model potential supply disruptions.** Regulatory authorities should review the risk for supply chain disruption for critically-needed medicines based on their country's epidemiology. Consider developing a supply chain vulnerability risk assessment that will model hypothetical situations for future disruptions.

3. **Design strategies for rapid response.** Consider establishing supply disruption mitigation teams to rapidly respond to major supply chain disruptions. The teams, which can meet virtually, will map sources of supply for the country's pharmaceutical value chain, report on immediate or potential impact, and advise on mitigation strategies.

4. **Develop recommendations for the local pharmaceutical industry.** Regulatory authorities should recommend actions to reduce manufacturing disruptions related to potential issues such as limited staff, supply disruptions for active pharmaceutical ingredients (APIs) and inactive ingredients (excipients), equipment failures, and spike in demand for medical products essential to the COVID-19 response.

Share information during COVID-19 pandemic

1. **Communicate medical product shortages.** Regulatory authorities should provide periodic communication to their citizens on the shortages that have been identified and how they are being mitigated.

2. **Share updates on prevention and treatment options for COVID-19.** Regulatory agencies have the responsibility to communicate to the public the current lack of effective prevention and treatment options for COVID-19, while at the same time informing the public about ongoing vaccine trials, provider/patient agreements to use experimental therapeutic options, and compassionate use of products currently undergoing regulatory review.

3. **Capture treatment outcomes.** Encourage physicians, nurses, and pharmacists to report outcomes on the use of any therapeutic products in COVID-19 patients. Health workers can use current electronic pharmacovigilance reporting systems.

4. **Rely on existing regulatory networks and regional harmonization initiatives.** Regulatory authorities in low- and middle-income countries should build on previous collaboration to share both confidential and public information expeditiously, enabling timely local decision making.

Protect patients from substandard and falsified medical products

1. **Share product quality surveillance information.** Develop systems to share inspection reports, product quality test results, and other data relevant to medical product quality with other regulatory agencies.

2. **Implement risk-based quality surveillance.** Potential therapeutic options for COVID-19 may become a new focus for falsified medicines and substandard manufacturing and should be prioritized for quality surveillance. Such products may include chloroquine, hydroxychloroquine, azithromycin, lopinavir/ritonavir, ribavirin, and corticosteroids. Consult the Guidance for Implementing Risk-Based Post-Marketing Quality Surveillance in Low- and Middle-Income Countries developed by the Promoting the Quality of Medicines program, which was implemented by USP and funded by USAID.

3. **Leverage technology to remotely monitor medical product quality.** Strategies may include analyzing multiple data points, such as social media for insights into product quality, patient reporting, and serialization and track and trace technologies. During pandemics, inspectors are unable to travel, and quality control labs are unable to test products in a timely manner. Remote surveillance capabilities will help protect the public from poor-quality medical products.

[1] Shoman, H., Karafillakis, E., & Rawaf, S. (2017). The link between the West African Ebola outbreak and health systems in Guinea, Liberia and Sierra Leone: a systematic review. Globalization and health, 13(1), 1. https://doi.org/10.1186/s12992-016-0224-2

[2] Article 13:2 of the AU Model law The Agency/Authority may from time to time determine that a medical product or category of medical products or part of any class or category of medical products shall be subject to exemption from marketing authorization in terms of this law.

[3] Provide a notice to remind manufacturers of those requirements where they exist. For instance, South Africa section 19(2) of the Medicines and related Substances Act (Act 101 of 1965) as amended, requires manufacturers to notify SAHPRA of any anticipated disruptions in supply, any shortages of products experienced, and any planned withdrawals of products from the market.

Establish policies to mitigate future shortages

1. **Gather information on potential shortages.** Establish policy for manufacturers to share information on shortages more transparently, disclose reasons for supply chain disruptions, and develop timelines for their resolution. Revise regulations to require manufacturers to submit information on manufacturer location, batch size, current capacity, etc. Regulators can also utilize information contained in the Drug Master File (DMF) to better inform the public on imminent shortages and vulnerability to supply disruption.

2. **Develop a categorization system for shortage-prone products.** Shortage-prone products are already a subset of the country's Essential Medicines List (EML) products but may be further delineated as vital/critical/life-saving and non-critical.

3. **Establish policies for shortage-prone products:** Establish policies for mandatory reporting of shortages by industry, controlled importation of foreign-approved products, and fast-track review for shortage-prone products.

4. **Incentivize manufacturing of shortage-prone medical products.** Consider strategies such as financial incentives, long-term procurement contracts, advanced market commitments, and government stockpiling.

5. **Revise regulations to establish National Drug Code and serialization systems.** Enable tracking of distribution and traceability. Contribute to global efforts towards unique global product identification.

6. **Support innovation in manufacturing.** Develop agile and flexible regulatory mechanisms. Provide regulatory support and incentives for manufacturers that are deploying leap-frog technologies including continuous manufacturing.

7. **Enable efficient product development during health emergencies.** Develop guidelines for pragmatic clinical trials and design of Real-World Evidence studies to support the re-purposing of approved products during health emergencies.

8. **Consider emergency use of medical products.** Develop guidance on regulatory preparedness for emergency use authorization and ethical principles for ensuring medical product quality assurance during disease outbreaks. Many countries currently do not have the regulatory tools to use new products or formulations during health emergencies. Regulators should continue to seek guidance from the World Health Organization on emergency use of medical products during public health emergencies.