

IGBA DRUG SHORTAGES WORKSTREAM

Report to the World Health Organization

NOVEMBER 2022

IGBA | INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

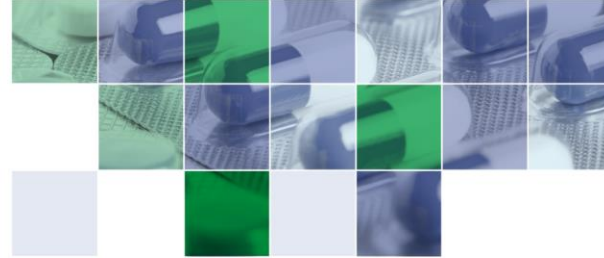
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The International Generic and Biosimilar medicines Association (IGBA) strengthens cooperation between associations representing manufacturers of generic and biosimilar medicines from around the world. The IGBA is at the forefront of preserving sustainable competition within our industry, by stimulating competitiveness and innovation in the pharmaceutical sector; thereby, ensuring millions of patients around the world have access to high quality, pro-competitive medicines.



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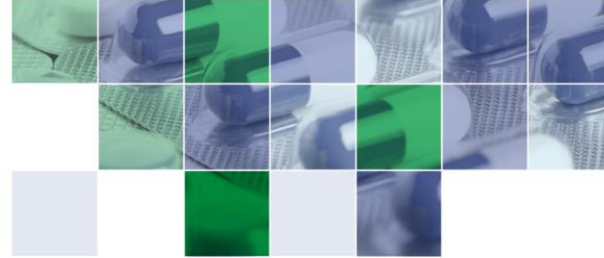
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1.0 Executive Summary

The purpose of this document is to report on the progress made under the IGBA-WHO collaboration plan to support the WHO's technical work on supply chain capacity to mitigate drug shortages affecting essential medicines. The group experienced challenges to collect verifiable market data on shortages of priority injectable antibiotics and injectable oncology drugs that are critical to health care delivery among WHO-targeted Low and Middle-Income Countries (LMICs). Therefore, as an alternative at this juncture, this report discusses existing factors that threaten the continued supply of generic medicines, including poor procurement practices, manufacturing consolidation and issues leading to shortages, regulatory hurdles and the impact of local policy changes on a globalized industry. Potential policy considerations to address these issues are proposed to inform WHO outreach to LMIC markets to encourage the adoption of strategies prevent and mitigate drug shortages.

2.0 Background

The following report was prepared as part of the agreed upon work identified in the **Collaboration Plan between WHO and International Generic and Biosimilar Medicines Association (IGBA) for the period 2022-2024 for an application to official relations with WHO.**

2.1 Objective of the WHO-IGBA Drug Shortages Workstream

Provide technical information, data and/or other evidence as requested, to inform WHO's technical work on supply chain capacity as well as on shortages affecting essential medicines, including products affected by COVID-19 and those related to priorities of the Access to COVID-19 Tools (ACT-A) Accelerator activities. The activities aim to support WHO's efforts towards improving availability and quality of information from medicines supply chains, shortages reporting and other innovative areas to reduce the negative impact of suboptimal supply chain performance.

2.2 Activities

1. *At WHO's request, collect and provide relevant technical information on medicines in shortage to inform WHO's work, as appropriate, including WHO's biweekly reports on products impacted by COVID-19, shortages reporting mechanisms, and other WHO's analyses conducted on medicines shortages, their causes and mitigation.*
2. *With guidance from WHO, collect, and analyze technical information, data and/or other evidence that may cause chronic shortages of medicines, focused on selected generic medicines identified by WHO.*

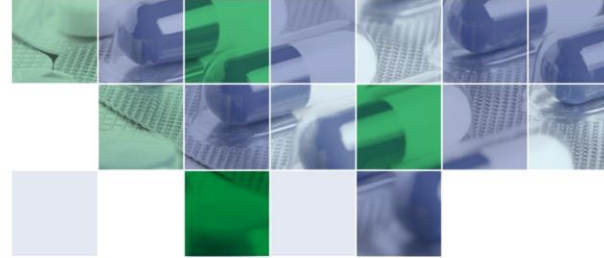
2.3 Outputs

Collected data and analysis to support the writing of a report for submission to WHO.

2.4 Overview of IGBA- WHO Collaboration on Drug Shortages

The IGBA and WHO have been working together since October 2020 to establish collaboration plan for 2022-2024 to support the WHO's strategic priorities related to drug shortages. The WHO is invested in minimizing and preventing drug shortages through the identification of root causes and implementation of appropriate control strategies.

Tracking and interpreting shortage data globally is a challenge due to varying definitions for "shortages" and approaches for tracking drug shortages. There are over 100 different definitions for drug shortages globally. There is varying availability of voluntary or mandatory drug shortages tracking systems, which lack uniformity and consistency for the scope products being tracked. For example, some jurisdictions only track a subset of drugs, like critical drugs, whereas others track all drugs. This leads to challenges using and interpreting the data and identifying trends across jurisdictions or subsets of the market, like for single sourced products vs. multi-sourced products, the latter of which are typically generic drugs.



It proved challenging to identify the best way IGBA could contribute to the situation, without duplicating existing efforts, while providing value to both the WHO and IGBA members. IGBA's contribution was suggested as providing WHO with verifiable market data including references on shortages, including select molecules on Essential Medicines Lists (EML). It was also recommended to study and compare market concentration and to consolidate the results with policies that impact market concentration.

It was agreed that IGBA would focus its efforts on critical medicines that are chronically in shortage such as injectable oncology and antibiotic medicines and identify and examine root causes of shortages and propose potential mitigation strategies through the development of case studies, where appropriate. Based upon historical shortage evidence available to the WHO it was agreed that the following medicines would be investigated: Erwinase, Ciprofloxacin, Vancomycin, Gentamicin, Piperacillin, Erythromycin, Clindamycin, Heparin. These medicines are critical for patient care. Vancomycin is the antibiotic of last resort especially for sepsis. Piperacillin tazobactam is a highly specialised hospital antibiotic and not easily substitutable. Finally, heparin plays a critical role in some treatments and there are limited alternative anti-coagulant alternatives for some surgeries.

The susceptibility to shortages of the above molecules is further compounded by the ongoing threat of antimicrobial resistance (AMR). The WHO has declared AMR to be one of the top 10 global public health threats facing humanity¹. Further, according to WHO research "*The clinical pipeline of new antimicrobials is dry. In 2019 WHO identified 32 antibiotics in clinical development that address the WHO list of priority pathogens, of which only six were classified as innovative. Furthermore, a lack of access to quality antimicrobials remains a major issue. Antibiotic shortages are affecting countries of all levels of development and especially in health-care systems.*" For example, data from countries reporting to the *Global Antimicrobial Resistance and Use Surveillance System (GLASS)* show that resistance to ciprofloxacin varies from 8.4% to 92.9% for *Escherichia coli* and from 4.1% to 79.4% for *Klebsiella pneumoniae*².

The use and benefits of injectable medicines, including precise and adjustable dosing, predictable bioavailability, and fast onset of action, are complicated by the challenges inherent in the manufacture and distribution of this format.

Challenges posed by injectable medicines include:

- Overcoming additional regulatory requests for studies, and increasing costs of regulatory compliance,
- Manufacturing a unique technology and dosage form,
- Limited availability of manufacturing sites globally,
- Complexities of the injectable market where manufacturing and Good Manufacturing Practices (GMP) risks are very high due to the sterile nature of the production,
- Investments in infrastructure needed as a result of current vaccine delivery requirements that will benefit future products,
- Highly controlled distribution systems, where the temperature must be carefully controlled throughout the supply chain and supported by additional stability studies, the cost of which may prohibitive and exceed the price of the product three-fold in the example for a product shipped from Europe to Bangladesh,
- Difficulty in forecasting demand and ensuring supply of critical medicines, and;
- Low product margins may lead to fewer players, such that injectable oncology products could become the next 'antibiotics,' which are necessary medicines but lack of incentive to manufacture

2.5 Methodology and approach

IGBA began by compiling lists of injectable antibiotic and oncology medicines in shortage in various jurisdictions around the world to look for overlapping data and/or trends. Markets included USA, Canada, Japan, Belgium, France, Netherlands, Portugal, Spain and WHO data. See **Appendix 1: Current Shortages of Injectable Antibiotic & Injectable Oncology Drugs**.

¹ WHO: Antimicrobial resistance (Nov 2021) <https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance#:~:text=What%20is%20antimicrobial%20resistance%3F,sprea%2C%20severe%20illness%20and%20death>

² WHO: Global Antimicrobial Resistance and Use Surveillance System (GLASS Reptot), Early Implementation (2020) <https://apps.who.int/iris/rest/bitstreams/1277847/retrieve>



Very few medicines were listed as being in shortages and even fewer medicines that were common to multiple markets. Further it is challenging, based on the nature of reporting systems, the type of data reported and the definition of shortages in any given jurisdiction, to determine whether these are true shortages impacting patient safety or simply back orders and whether they are regional or have a national impact. In the UA, companies call the Food & Drug Administration (FDA) to inform them of impending shortages and then work together to try to mitigate them. Only actual shortages are posted on FDA's website. However, shortages may stay on the website well after the time they are resolved. Further, fewer shortages could be expected a free market such as the US where prices increase in times of limited supply, but this is not the case. Canada has mandatory reporting for any situation where market demand cannot be met, even if a company can supply their own customers. Thus, one would expect to see more shortages reported, though they may not be impacting patient access and safety. An escalation process has been implemented in Canada to identify reported shortages of concern to the public. Japan's Ministry of Health, Labour and Welfare (MHLW) does not post drug shortages. The E.U.'s database only reports on centrally approved products.

Following a discussion of the above information with the WHO, it was further clarified that the WHO was primarily interested in the shortage situations in Pakistan, Bangladesh, Brazil, Russia, India, China, and South Africa as indicators or predictors for other lower middle-income markets (LMICs).

IGBA member companies gathered internal data; however, in general, they do not sell into the targeted WHO markets and/or haven't experienced shortages in these markets. Available data is shown in **Appendix 2: Case Studies: Root causes of Multi-country Drug Shortages and Possible Mitigation Strategies**. The results of this analysis showed that no shortages were reported for the targeted injectable antibiotics and injectable oncology drugs in the above LMICs countries except for a brief shortage in 2022 for flu medication in Brazil, and a heparin shortage in India during the time period examined.

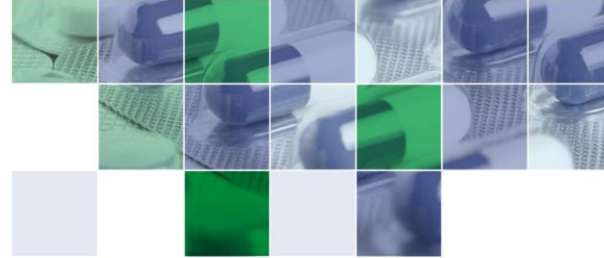
Given the lack of information for the identified molecules outlined in **Appendix 1** in the LMICs markets of interest to WHO (Pakistan, Bangladesh, Brazil, Russia, India, China, and South Africa) it was proposed that a paper be drafted to discuss some of the challenges with generic policies in general, which are outlined in section 3.0 and include:

- Poor procurement practices causing localised shortages (either in a region, a group of hospitals, or single country),
- Major manufacturing problems causing a global supply shortage,
- Regulatory hurdles, and;
- Difficult to predict issues causing a supply or cost issues.

3.0 Factors that impact the security and supply of generic medicines

3.1 Poor procurement practices leave hospitals or regions exposed to localised shortages

In most countries around the world, there has been a consolidation of how hospital products are purchased. In the US, pooled procurement is undertaken by hospital buyers. In Europe, hospital products are purchased by hospital buying groups (i.e., France) or by countries or regions (Denmark, Italian or Spanish regions). In Canada, hospital purchasing is controlled by two main group purchasing organizations, with the exception of the province of Quebec, where the purchasing is overseen by the provincial government. In Japan, major nationwide hospital chains and nationwide pharmacy chain groups impose heavy discount pressure on generic companies to leverage bulk buying power. In some cases, this consolidated procurement has been pursued with one objective, which is to lower prices with limited consideration for security of supply. For example, in Europe there tends to be very short lead times for tenders. For many antibiotics, there are capped prices (often at the final price of the previous tender that means prices can only go down over time) and it is rare to implement multi-winner tenders within consolidated procurement models. Moreover, hospitals make limited use of digital inventories and are generally poor at predicting demand. There are some limited experiments with multi-winner tenders in the UK, Italy and Denmark, Greece and Denmark. Of note, the UK suspended multi-winner hospital tendering for a few years and experienced widespread medicine shortages, which dropped considerably only after multi-winner tenders were reinstated. In the US, contracting can be unpredictable as buyers do not always commit to purchase from the tender winner. Buyers can also purchase from other suppliers if a lower price is offered, meaning that buyers make limited purchase commitments. The US hospital group CIVICA RX has changed its procurement policy notably for



vancomycin to offer purchasing commitments to encourage more secure supply. In Canada, Group Purchasing Organizations (GPO) issue Requests For Proposals (RFP) and award contracts to the winning bids. Awards are based on price, but also on security of supply and other quality factors. However, penalties are substantial if the market authorization holder is not able to meet demand, even if the demand exceeds what was projected. In Japan, the health authority, MHLW, categorized vancomycin as a “category A” product needed for special care of stable supply and is currently mapping the supply chain to identify the supply risk of the product.

The important lesson for lower income countries is that procurement is an important instrument to encourage price competition and to encourage supply security. The US FDA³ and a study for the European Commission⁴ both concluded the hospital tender reform is needed to reduce shortages of medicines and to de-consolidate the off-patent pharmaceutical sector. Market predictability and viability are essential to ensure secure supply of medicines. Due to the global consolidated nature of the pharmaceutical market, governments need to look beyond localized shortages and supply to consider the impact on the global market. Most producers selling the same product into multiple markets and thus poor procurement practices in one jurisdiction have a broader impact on the availability of product supply across markets.

3.2 Generic manufacturing issues leading to shortages reflect consolidation within the manufacturing supply chain caused by market pressure on prices

Although poor procurement practices described in Section 3.1 have led to market consolidation and should be an area of focus to sustain the viability of current markets, once progress in this area have been made, governments should explore complimentary policies to encourage manufacturing and the diversification of the supply chain to support market growth.

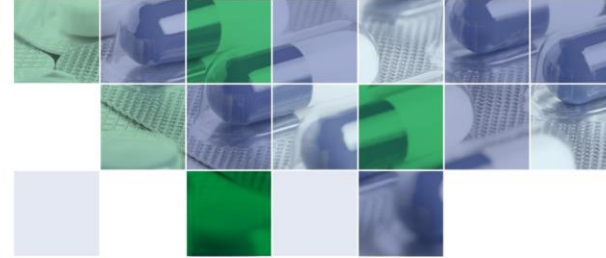
Markets relying on consolidated sources of active pharmaceutical ingredients suppliers are often threatened as seen during the recent pandemic when India restricted the export of certain key drugs and ingredients to look after their domestic market needs first. Shortages of antibiotics, including piperacillin tazobactam, and heparin shortages have been caused by manufacturing problems of the finished dosage form or the critical raw materials used to manufacture the active pharmaceutical ingredients. There are only a limited number of global manufacturers and many of them are based in China or India. If one manufacturer is faced with a challenge that impacts production (e.g., an explosion at a factory for piperacillin, or an African Swine Flu outbreak in Chinese pig farms) the net result may be a global shortage. The problem is not the location where the material is produced but that there are so few alternative manufacturers/suppliers to turn to in the event of a gap in supply. This is a sign of consolidation of the manufacturing supply chain for critical medicines.

Since consolidation along the manufacturing supply chain is a major risk for critical medicines, it would make sense to consider ways to de-consolidate and to diversify the supply chain. While encouraging the development of local suppliers, the infant formula shortage in the US throughout 2022 has demonstrated that local production alone does not protect from shortages if the market is globally consolidated. The challenge is that almost all generic hospital products markets are heavily commoditised due to consolidated procurement, as described in section 3.1. Until the viability of current markets can be strengthened it remains challenging for manufacturers to invest in diversification and growth. Governments should be encouraged to introduce policies to incentivize investment in manufacturing. Such incentives could be designed to diversify production, like the Indian industrial policy measures to expand antibiotic ingredient production. Governments could also be encouraged to collect data on supply chain consolidation, which may be available to regulators, to influence market reforms to de-commoditise the markets for these medicines, particularly for critical medicines like antibiotics. For example, the level of consolidation for a given group of molecules could be assessed to determine how many manufactures source from the same supplier or region to inform incentives to source from other suppliers or regions.

We underline that temporary subsidies will not solve fundamental flaws in markets that are driving industry consolidation. Therefore, any such support for manufacturing should include measures to encourage

³ FDA, Report, Drug Shortages: Root Causes and Potential solutions (Oct 2019, Updated Feb 2020) <https://www.fda.gov/drugs/drug-shortages/report-drug-shortages-root-causes-and-potential-solutions>

⁴ Directorate-General for Food and Health Safety: European Commission: Future-proofing pharmaceutical legislation. Study on medicine shortages: Final report (revised) (Dec 2021) <https://op.europa.eu/en/publication-detail/-/publication/1f8185d5-5325-11ec-91ac-01aa75ed71a1/language-en/format-PDF/source-245338952>



multisource competition, introducing multi-winner tenders or modulations to reference price systems such as the Canadian “ladder” reference price system where prices predictably decrease when there are many suppliers and increase when there are few suppliers.

3.3 Regulatory hurdles, such as inflexibility in regulatory processes, lack of policies, and unavailability of communication among stakeholders can be addressed through global regulatory reliance, and ultimately, harmonization

The lack of harmonized regulations and policies globally impacts the introduction of new products and the sustainability of older generic medicines and limits competition. Harmonization allows generic medicines manufacturers to face fewer regulatory barriers and a lesser financial burden with the ultimate effect of easier and more rapid market access thus increasing competition. Conversely, increasing country-specific regulatory requirements, while intended to improve patient safety, will lead to a rationalization of product portfolios, often leading to product discontinuations and ultimately shortages due to a lack of competition. For example, since 2010, nearly 2,300 generic medicines have been discontinued and nearly 600 medicines shortages have occurred in the US.⁵

In South Africa, the registration of a new product could take up to 10 years if it is not prioritized by the regulator. In Bangladesh, there is no local registration of products; these products are registered and supplied by foreign markets. Allocation to markets where the need is higher is often hindered by regulatory barriers, like country specific regulatory requirements, the need for translation of labels, differences in healthcare practitioner information, and regulatory differences that lead to the need for different formats or dosage forms.

The generic pharmaceutical industry applauds regulatory efforts to increase the safety and accessibility of medicines around the world. However, greater emphasis should be placed on regulatory harmonization while we work towards the goal of increasing mutual reliance of inspections and decision making amongst global regulators.

3.4 Local policy changes can impact supplies in a globalised industry

Other policy factors can disrupt supplies. In some emerging markets, procurement contracts afford a preference to local manufacturers (i.e., 50% of the market is reserved for local manufacturers, the other 50% is open to international competition). However, there may be limited trust in the quality of locally manufactured products by prescribers, like in a countries that does not enforce GMPs. This can drive up demand for imported medicines and cause a shortage, which has been the case in Vietnam as only 50% of the demand can be met.

In Japan, where local pricing policy changed to an annual price revision from a biannual process, reduced manufacturing capability for international and domestic markets. Capital expenditures are needed facilitate compliance with the latest GMP requirements, which is getting harder to sustain for generic manufacturers.

Environmental policy is supported by the generic pharmaceutical industry, but it can also have an impact on the production of certain medicines, including antibiotics. China’s environmental policy has had a significant impact on the supply of raw materials for many medicines. European environmental or food safety policies can also have a disruptive impact on older molecules as many excipients are used in both food and pharmaceuticals. These policies are not specific to pharmaceuticals, but they broadly affect other sectors (chemicals, food) which limit options for predictable pharmaceutical supply. For LMIC countries, these policies can materially impact on the price of pharmaceuticals and the cost of goods that make marginal products unsustainable.

To better control anti-microbial resistance (AMR), the WHO and national public health authorities are implementing strategies to reduce the over or unnecessary prescription of antibiotics as this is a leading cause of resistance. The challenge for antibiotic manufacturers is that this will reduce the volume of sales over time. In practice, almost all regulated and semi-regulated markets have policies or market structures to maintain antibiotic prices at low levels. This drives the market to a rather unsustainable model of lower volumes and lower prices for antibiotic manufacturers. This will drive further consolidation of manufacturing

⁵ IGBA Position Paper: Medicines Shortages (2017)

https://www.igbamedicines.org/doc/2017_IGBA%20Position%20on%20Medicines%20Shortages.pdf



and make it more difficult for manufacturers to invest in the necessary upgrade of production sites for compliance with GMP and other regulatory obligations of the future such as improved environmental management. It is important to highlight that while the WHO or other public health institutions recognise and act to address the market failure of novel antibiotic development, there is almost no interest by these institutions to address the growing market failure of the well-established antibiotic medicine market. For example, a recent study⁶ by the Access to Medicines foundation shows that manufacturer corporate social responsibility projects are the main driver of policies to improve the availability of essential antibiotic medicines to lower income countries. There is almost no government support for these efforts. This contrasts with the efforts of many governments to directly finance the development of novel antibiotic medicines for the innovator industry confirming the inherent bias of most pharmaceutical policies that favour policies for the originator industry over the generic industry.

With regard to antibiotic molecules, there is a necessity to rethink market models as more and more countries introduce prescribing controls to reduce the risk of AMR. This necessitates a new approach to generic antibiotic markets that also encourages the maintenance of lower volume antibiotic molecules so as to maintain a wide range of molecule choices for prescribers. Already in Europe, there is a dramatic reduction in molecule options which is a risk in case of an AMR development with bigger volume antibiotic molecules.

3.5 Addressing barriers to allow for rapid reallocation of supply to meet cross-border needs

One challenge facing some of emerging markets may be related to limited allocation of stock in a global manufacturing shortage event. During Covid-19, the pharmaceutical industry experienced extreme policy efforts by governments to hoard medicines against global solidarity. IGBA is firmly opposed to these policies that may undermine the global solidarity that public health should demand. However, even under normal shortage policy measures, some of these countries can be affected in a shortage event. For example, most countries will not allow the export of medicines labelled (manufactured specifically) for their market to any other market. These types of controls exist even inside the European Union (restriction on 'parallel trade') because regulators will intervene to ensure appropriate allocation to hospitals according to need and to prevent speculation in the pharmaceutical distribution chain. We underline that this is not an export control on all manufactured products in the country but only a restriction on distribution (wholesaler exports) of products labelled for that market. In some countries, like Bangladesh, these medicines do not hold a national pharmaceutical licence therefore there is no production in the formal regulatory sense for Bangladesh. Rather, the country relies on imports of products licenced in other markets. In a shortage situation, it is unlikely that Bangladesh could continue to rely on the import of products licenced for another market. This suggests that the WHO could assist or encourage countries to promote the licencing of critical medicines in their market to address this risk.

Other regulatory factors can undermine efficient allocation in a crisis, namely labelling and patient information. Some manufacturers may have excess stock that could be sent to another market, but it can be very complex and costly to repackage medicines to meet the requirements of another market. In a shortage situation, regulators should have ready-made flexibilities to enable an efficient reallocation based on patient need. For example, during Covid-19, most countries and the EU enabled significant packaging/product information flexibility to facilitate cross-border allocation (i.e., in the EU covid vaccines had a common pack and electronic patient information). In addition, some structural measures such as electronic patient information leaflets would go a long way to removing this kind of challenge.

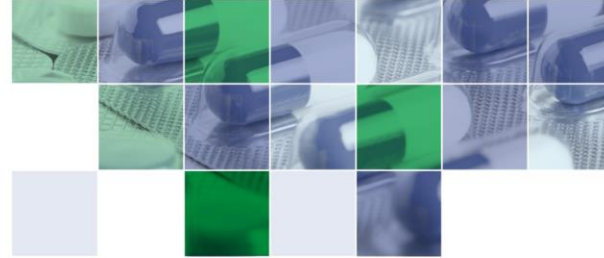
The IGBA has proposed measures to increase global regulatory cooperation, notably acceptance of global development, that would enable generic medicine developers to develop medicines on a global scale. This would improve shortage mitigation as medicines could be developed for multiple regions/countries and approved on the basis of the same clinical and scientific evidence. Consequently, medicine agencies would have access to a wider pool of products to potentially import in a shortage. This would simplify the regulatory oversight for medicine agencies to enact measures such as temporary imports.

⁶ Access to Medicine Foundation: Drug Makers must address access to antibiotics to help slow the superbug threat (June 2022). <https://accesstomedicinefoundation.org/news/drug-makers-must-address-access-to-antibiotics-to-help-slow-the-superbug-threat>



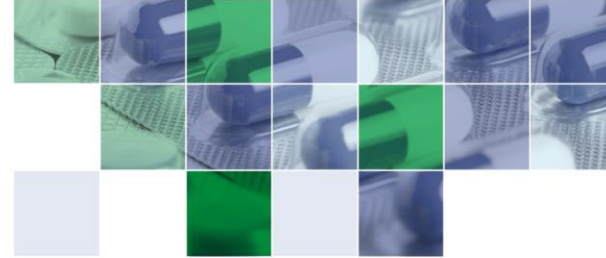
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4.0 Next steps

IGBA will continue to work closely with WHO to advance the 2022-2024 Collaboration Plan and support the WHO's strategic priorities related to drug shortages, including opportunity to further the activities listed in section 2.2 and discuss considerations related to support national medicines traceability systems.



Appendix 1: List of 2021 shortages of injectable antibiotic and oncology drugs (May 2021)

Table A: Injectable Oncology Products

<i>Injectable Oncology</i>	<i>Canada</i>	<i>USA</i>	<i>Japan</i>	<i>Belgium</i>	<i>France⁷</i>	<i>Netherlands</i>	<i>Portugal</i>	<i>Spain</i>	<i>WHO</i>
Amifostine Injection		X		N/A			N/A	Marketing suspended	
Asparaginase Erwinia Crysanthemi		X		N/A			N/A	N/A	
Azacitidine for Injection		X			X (1 brand)			X (1 brand, 4 alternatives)	
Dexamethasone Sodium Phosphate Injection		X			X (1 brand)				
Floxuridine for Injection		X		N/A			N/A	N/A	
Leucovorin Calcium Lophilized Powder for Injection		X		N/A			N/A	N/A	
Leuprolide Acetate Injection		X					X (No generic)	X (1 brand, 8 alternatives)	
Paclitaxel	X			X (1 brand, 5 alternatives)	X (2 brands)	X (2 brands)	X (1 brand, 4 alternatives)	X (1 brand, 6 alternatives)	
Methotrexate				X (2 brands)	X (2 brands)	X (1 brand)	X (2 injectable brands, 16 alternatives as pre-filled syringe + 5 injectable)	X (1 brand, 50+ alternatives)	

⁷ France lists detailed information about shortages per brand and indicates a shortage (“stock out”), a tension in the market (this allows the regulator to control allocation to say hospitals or a percentage of previous sales for wholesalers or pharmacists), a product is available again or when a product has been withdrawn. It does not indicate market shortages. Even for amoxiclav, some of the brands reported a stock out, other reported product available on the market again. This is likely to due high consumption of amoxiclav in hospitals at the moment generating stock outs with some manufacturers while others are bringing in stock to solve the problem quickly.



Table B: Injectable Antibiotics

Injectable Antibiotic	Canada	USA	Japan	Belgium	France⁸	Netherlands	Portugal	Spain	WHO
Acyclovir	X								
amoxiclav					X (6 brands)			X (1 brand, 5 alternatives)	X
Ampicillin									
Azithromycin									X
Cefazolin Injection		X		X (1 brand, marketing suspended)					
Cefmetazole				N/A			N/A	N/A	
Cefotaxime Sodium Injection		X				1 brand			
Cefotetan Disodium Injection		X		N/A			N/A	N/A	
Cefoxitin for Injection		X		N/A			N/A		
Ceftazidime and Avibactam (AVYCAZ®) for Injection, 2 grams/0.5 grams		X					No generic	No generic	
Ceftolozane and Tazobactam (Zerbaxa) Injection		X		N/A		X	X (No generic)	X (No generic)	
Imipenem and Cilastatin for Injection		X		N/A					
Isoniazid Injection USP		X		N/A			No generics	No generics	
Levofloxacin			X				X (1 brand – 3 alternatives)		X
Meropenem			X				X (1 brand, 13 alternatives)		
Metronidazole									X
Piperacillin				N/A (Only Piperacillin – Tazobactam combination : no shortages)	X (1 brand)		N/A (Only Piperacillin – Tazobactam combination, 7 alternatives)	N/A (Only Piperacillin – Tazobactam combination , 1 brand short, 11 alternatives)	X
Rifampin Injection		X		N/A			N/A	No generics	
Sulbactam				N/A			N/A	N/A	
Tazobactam				N/A (See piperacillin above)			N/A (See piperacillin above) Ceftolozane-Tazobactam combination short, no generic)	N/A (See piperacillin above) Ceftolozane-Tazobactam combination short, no generic)	X
Vancomycin			X	X (1 brand)			X (2 brands, 7 alternatives)	X (1 brand, 7 alternatives)	

⁸ France lists detailed information about shortages per brand and indicates a shortage (“stock out”), a tension in the market (this allows the regulator to control allocation to say hospitals or a percentage of previous sales for wholesalers or pharmacists), a product is available again or when a product has been withdrawn. It does not indicate market shortages. Even for amoxiclav, some of the brands reported a stock out, other reported product available on the market again. This is likely to due high consumption of amoxiclav in hospitals at the moment generating stock outs with some manufacturers while others are bringing in stock to solve the problem quickly.



Appendix 2: Case studies: Root cases of Multi-country Drug Shortages and Possible Mitigation Strategies

Medicine	Background, History of Drug, Shortages	Low to middle Income Countries Impacted by Shortages	Manufacturing Capacity / Technology; API sources	Distribution Challenges	Procurement Practices/ Pricing Regimes	Regulatory Challenges; Definition of Shortage	Sources of Information - Lead
Erwinase	Not registered in Bangladesh by local regulatory authority - Directorate General of Drug Administration (DGDA), Bangladesh	N/A	N/A	N/A	N/A	N/A	N/A
Ciprofloxacin	<p>Ciprofloxacin was approved in Bangladesh in 1986. Total market size of this generic is BDT 14,731,87,922</p> <p>Almost 110 companies are manufacturing Ciprofloxacin as tablets, capsules, PFS, sachet, IV injection, eye and ear drops</p> <p>No supply shortage of Ciprofloxacin in Bangladesh pharma market</p>	Plenty available; there is no impact by shortage.	<p>Capacity/Technology: Sufficient manufacturing capacity in Bangladesh</p> <p>API Source: China, India</p>	No challenges	As per DGDA guideline	No challenges	<ul style="list-style-type: none"> • DGDA • IQVIA
Vancomycin	<p>Vancomycin is registered in Bangladesh since 1997</p> <p>Total nine (09) pharmaceuticals companies are manufacturing/marketing this product as IV injection in Bangladesh</p> <p>No supply</p>	Plenty available; there is no impact by shortage.	<p>Capacity/Technology: Sufficient manufacturing capacity in Bangladesh</p> <p>API Source: India</p>	No challenges	As per DGDA guideline	No challenges	<ul style="list-style-type: none"> • DGDA • IQVIA



Medicine	Background, History of Drug, Shortages	Low to middle Income Countries Impacted by Shortages	Manufacturing Capacity / Technology; API sources	Distribution Challenges	Procurement Practices/ Pricing Regimes	Regulatory Challenges; Definition of Shortage	Sources of Information - Lead
	shortage in Bangladesh pharma market						
Gentamicin	<p>This product is available in Bangladesh since 1984</p> <p>Total 43 Pharmaceutical companies are manufacturing this product in Bangladesh as injection, cream etc.</p> <p>No supply shortage in Bangladesh pharma market</p>	Plenty available; there is no impact by shortage.	<p>Capacity/Technology: Plenty of manufacturing capacity available</p> <p>API Source: South Korea and others</p>	No challenges	As per DGDA guideline	No challenges	<ul style="list-style-type: none"> DGDA IQVIA
Piperacillin	<p>Piperacillin + Tazobactam combination is registered in Bangladesh since 2009</p> <p>Total seven brands are available in Bangladesh as IV injection</p> <p>No supply shortage in Bangladesh pharma market</p>	Plenty available; there is no impact by shortage	<p>Capacity/Technology: Adequate manufacturing capacity in Bangladesh</p> <p>API Source: India, China</p>	No challenges	As per DGDA guideline	No challenges	<ul style="list-style-type: none"> DGDA IQVIA
Erythromycin	<p>This product is available in Bangladesh since 1982</p> <p>Total 70 Pharmaceutical companies have taken registration as tablet, PFS, paediatric drops, cream and lotion in Bangladesh</p> <p>No supply shortage in Bangladesh pharma</p>	Plenty available; there is no impact by shortage	<p>Capacity/Technology: Plenty of manufacturing capacity available</p> <p>API Source: China, Thailand, India</p>	No challenges	As per DGDA guideline	No challenges	<ul style="list-style-type: none"> DGDA IQVIA



Medicine	Background, History of Drug, Shortages	Low to middle Income Countries Impacted by Shortages	Manufacturing Capacity / Technology; API sources	Distribution Challenges	Procurement Practices/ Pricing Regimes	Regulatory Challenges; Definition of Shortage	Sources of Information - Lead
	market						
Clindamycin	<p>Clindamycin is available in Bangladesh since 2001</p> <p>Total market size in Bangladesh is BDT 44,84,84,424</p> <p>Total 38 brands are available in Bangladesh as capsule, injection, lotion and gel</p> <p>No supply shortage in Bangladesh pharma market</p>	Plenty available; there is no impact by shortage	<p>Capacity/Technology: Plenty of manufacturing capacity available</p> <p>API Source: China</p>	No challenges	As per DGDA guideline	No challenges	<ul style="list-style-type: none"> • DGDA • IQVIA
Heparin	<p>Heparin was approved in DCC (Drug Control Committee) of Bangladesh in the year 1987</p> <p>Total five (05) pharmaceutical companies have taken registration in Bangladesh as IV injection</p> <p>No supply shortage in Bangladesh pharma market</p>	There is no impact by shortage	<p>Capacity/Technology: Available</p> <p>API Source: UK, Denmark</p>	No challenges	As per DGDA guideline	No challenges	<ul style="list-style-type: none"> • DGDA • IQVIA



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