Promoting the Quality of Medicines Plus (PQM+)

Neglected Tropical Diseases Medical Products Market Landscape and Bulk Procurement Sources: Executive Summary

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About PQM+

The Promoting the Quality of Medicines Plus (PQM+) Program is a six-year cooperative agreement between USAID and USP to sustainably strengthen medical product quality assurance systems in low- and middle-income countries. The program works to improve medical product quality through cross-sectoral and systems strengthening approaches and the application of international quality assurance standards across the pharmaceutical system. By sharing scientific expertise and providing technical support and leadership, PQM+ helps create resilient and robust local health systems that address diseases such as HIV/AIDS, tuberculosis, malaria, and neglected tropical diseases, as well as improve maternal, newborn, and child health.

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Contents

Acronyms

API	active pharmaceutical ingredient
ASEAN	Association of Southeast Asian Nations
DRC	Democratic Republic of the Congo
EMA	European Medicines Agency
EML	WHO Model List of Essential Medicines
FPP	finished pharmaceutical product
GMP	good manufacturing practice
LMIC	low- / middle-income country
MDA	mass drug administration
ML	maturity level
NRA	national regulatory authority
NTD	neglected tropical disease
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PQ	prequalification
PQM+	Promoting the Quality of Medicines Plus program
SRA	stringent regulatory authority
USAID	U.S. Agency for International Development
USFDA	U.S. Food and Drug Administration
USP	U.S. Pharmacopeial Convention
WHO	World Health Organization

Background

Neglected tropical diseases (NTDs) are communicable infectious illnesses associated mostly with poverty. These illnesses include 20 diseases and disease groups that affect more than one billion people worldwide living in the most impoverished conditions, mostly in tropical and subtropical regions.[1] The human impact of NTDs varies depending on the type and severity of the disease. Some NTDs, such as dengue hemorrhagic fever, can be fatal,[2] while others can cause irreversible disabilities, such as blindness and disfigurement.[3] Social impacts of the less severe NTDs—particularly those that primarily affect children—can lead to growth retardation, interrupt education, and place significant burdens on families and communities supporting infected individuals.[4] As a result, NTDs aggravate the cycle of poverty among the world's underprivileged and marginalized populations. The social and economic burden of NTDs on population health is tremendous and requires serious attention on a global scale.[5] More than 2.7 billion of the most impoverished people across Africa, Asia, and Latin America are affected. Therefore, effective control and elimination of NTDs constitutes an important step toward achieving sustainable development goals.

Climate zones in sub-Saharan Africa and South and Southeast Asia range from hot desert to rainy forest, creating favorable conditions for the growth of many disease-causing organisms and their vectors, including those responsible for NTDs. Such conditions create stability challenges for drug formulations that are sensitive to temperature and moisture and require special storage and transportation conditions for medical products.

Mounting effective control and/or elimination of NTDs requires both nonpharmacological and pharmacological interventions. For pharmacological interventions (such as preventive chemotherapy, transmission control, and treatment of infected patients), the availability of safe, effective, and quality-assured drugs distributed according to World Health Organization (WHO) treatment guidelines is paramount to reducing morbidity.[6] An adequate and strong supply chain of quality-assured NTD drugs enables countries to implement both large-scale preventive chemotherapy and treatment of infected patients.

NTDs disproportionately affect low- and middle-income countries (LMICs), where key regulatory authorities, medicine quality assurance systems, and manufacturing capacity are still developing. As a result, the current global supply chain of NTD medicines relies in large part on donation programs targeting a narrow group of specific diseases. These programs are unlikely

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[1] Montresor A, Gabrielli AF, Chitsulo L, Ichimori K, Mariotti S, Engels D, et al. Preventive chemotherapy and the fight against neglected tropical diseases. Expert Review of Anti-Infective Therapy. 2012. pp. 237–242. doi: https://doi.org/10.1586/eri.11.165.

[2] Zeng Z, Zhan J, Chen L, Chen H, Cheng S. Global, regional, and national dengue burden from 1990 to 2017: A systematic analysis based on the global burden of disease study 2017. EClinicalMedicine 2021;32:100712. doi: https://doi.org/10.1016/j.eclinm.2020.100712.

[3] Coffeng LE, Stolk WA, Zoure HG, et al. African programme for onchocerciasis control 1995-2015: updated health impact estimates based on new disability weights. PLoS Negl Trop Dis 2014;8(6):e2759. doi: https://doi.org/10.1371/journal.pntd.0002759.

[4] Weatherhead JE, Hotez PJ, Mejia R. The Global State of Helminth Control and Elimination in Children. Pediatr Clin North Am 2017;64(4):867-877. doi: https://doi.org/10.1016/j.pcl.2017.03.005.

[5] Ochola EA, Karanja DMS, Elliott SJ (2021) The impact of Neglected Tropical Diseases (NTDs) on health and wellbeing in sub-Saharan Africa (SSA): A case study of Kenya. PLoS Negl Trop Dis 15(2): e0009131. https://doi.org/10.1371/journal.pntd.0009131.

[6] Ending the neglect to attain the Sustainable Development Goals: A road map for neglected tropical diseases 2021–2030. Geneva: World Health Organization (WHO), 2021. Dowload at https://iris.who.int/bitstream/handle/10665/338565/9789240010352-eng.pdf?sequence=1.

to continue indefinitely. Therefore, it is crucial to improve local capacity to ensure access to safe, effective, quality-assured medical products for the long term. As a starting point, a situational analysis can provide context and help prioritize areas for investment/improvement for NTD supply chains, particularly local pharmaceutical production and supply chain capacity.

Objective

PQM+ assessed the supply chain of seven NTD drugs (albendazole, azithromycin, diethylcarbamazine, ivermectin, praziquantel, mebendazole, and tetracycline eye ointment) by surveying manufacturers throughout Asia and Africa.[7] The NTDs these drugs treat include lymphatic filariasis, soil-transmitted helminthiasis, schistosomiasis, onchocerciasis, and trachoma.

The current supply of NTD drugs (albendazole, azithromycin, diethylcarbamazine, ivermectin, praziquantel, mebendazole, and tetracycline eye ointment) relies in large part on donation programs targeting a narrow group of specific diseases.

The main objective of this landscape analysis was to support the U.S. Agency for International Development's (USAID) planning and programming efforts to increase local capacity for production and procurement of NTD medical products in Asia and sub-Saharan Africa. Additional objectives included creating awareness of existing NTD medicine manufacturers in these regions and understanding the limitations and opportunities within current regional supply chains for these targeted products.

The study focused on several key areas. First, it aimed to identify active pharmaceutical ingredient (API) and finished pharmaceutical product (FPP) manufacturers of NTD medical products in the targeted regions. Second, the study explored the manufacturing capacities, production operations, technical capabilities, quality assurance systems, bulk procurers, sources, and other business factors influencing the NTD product market in these regions.

Moreover, the study involved surveying the manufacturers with respect to good manufacturing practice (GMP) compliance. Lastly, it sought to pinpoint the existing supply chain gaps, strengths, and weaknesses in the Association of Southeast Asian Nations (ASEAN) as well as South Asian and African countries. By addressing these objectives, the analysis aimed to provide valuable insights to inform and improve USAID's strategies in the following key areas.

Key Findings and Recommendations

1. **Underutilized manufacturing capacity**: Both the Africa and Asia regions have manufacturers with ample capacity that is not fully utilized. These manufacturers are often operating on a small batch production model.
2. **Importance of regulatory compliance**: Lack of regulatory compliance with international GMP standards is a common impediment to growth in both regions. Achieving international standards is vital for market entry and sustainability.

[7] This document is a condensed version of PQM+ (2022) *Neglected Tropical Diseases Medical Products Market Landscape and Bulk Procurement Source*. Submitted to the U.S. Agency for International Development by the PQM+ Program. Rockville, MD: U.S. Pharmacopeial Convention.

3. **Need for technical support**: Technical support is essential for both manufacturers and regulatory agencies to overcome challenges and improve compliance with international standards.
4. **Opportunities for regional collaboration**: Both regions could benefit from regional coordination and collaboration to optimize manufacturing capacity, determine volume demands, and improve access to critical medicines.
5. **Recommendations**: Recommendations include building capacity for self-reliance, improving regulatory compliance and quality, and streamlining government incentives to support local NTD pharmaceutical manufacturers in both regions.

Results: NTD Medical Products Manufacturers in ASEAN and South Asia Countries

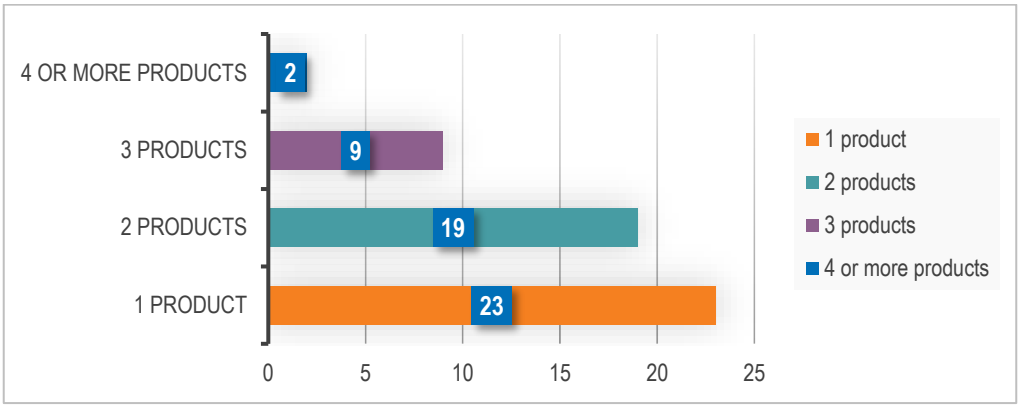
A Monash University team used online databases and contacted regulatory authorities within the targeted countries to compile a list of 308 NTD manufacturers. Further screening of the manufacturer list against criteria, such as active licenses, production currently in active status, and products manufactured for human use, resulted in 159 manufacturers eligible for inclusion in this study. The data in this report represent a final pool of 53 responding manufacturers, which is 33.3% of those eligible in the targeted countries (Table 1).

Table 1. Identified Manufacturers by Country and Their Survey Participation Rate

Country	No. of Eligible Manufacturers Identified	No. of Participating Manufacturers	No. of Manufactures that Declined	No. of manufacturers with No Response	Participation Rate (percent)
Bangladesh	16	9	0	7	56.3
Indonesia	19	5	5	9	26.3
Laos PDR	4	4	0	0	100
Malaysia	9	3	3	3	33.3
Myanmar	5	5	0	0	100
Nepal	28	4	0	24	14.3
Philippines	7	1	1	5	14.3
Thailand	35	21	3	11	60
Vietnam	36	1	0	35	2.8
Total	**159**	**53**	**12**	**94**	**33.3**

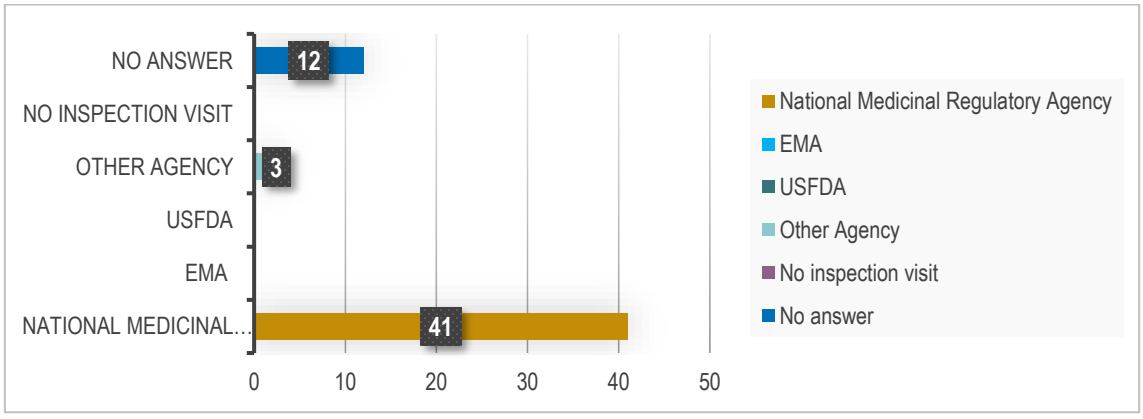
Of the 53 participating manufacturers, 79.3% manufacture one or two NTD products. The remaining 20.7% manufacture three or more NTD products (Figure 1).

Figure 1. Number of NTD Products Manufactured by the Manufacturers (N = 53)



The percentage of manufacturers receiving regulatory approvals is an indicator of the supply through authorized suppliers of NTD products within the region. Most manufacturers (77.4%) reported that their manufacturing sites have been inspected and approved by their respective countries' national regulatory agencies at least once within the past three years. Three manufacturers reported that other agencies performed the inspection and approval (Figure 2). None of the manufacturers had been inspected nor received approval from stringent regulatory authorities (SRAs) such as the U.S. Food and Drug Administration (USFDA) or European Medicines Agency (EMA). The outcome from an SRA assessment is more credible than one from a national regulatory authority (NRA) with a WHO maturity level (ML) at or below 3. Assessments from SRAs and higher ML country NRAs assure the ability of manufacturers to comply with or maintain GMP standards of safety, identity, strength, purity, and quality. Of the surveyed manufacturers, only four are located in countries where the NRAs meet ML3 (Ghana and Nigeria).

Figure 2. Number of Manufacturers with Sites Inspected and Approved by Regulatory Authorities in the Past 3 Years (N = 53)



As noted above, 77.4% of surveyed manufacturers met the compliance requirements of their NRAs for products to be considered quality assured and have received market authorization for their registered NTD products. Sixty percent of the surveyed manufacturers reported that they met all nine regulatory compliance items listed in Table 2.

Table 2. Manufacturers' Regulatory Compliance (N = 53)

Regulatory Compliance Requirements	Complied	Not Complied	No Answer
Manufacturing license issued by the national authority	100%	0%	0%
GMPs certified by health authority	96%	4%	0%
Site master file current	96%	4%	0%
List of authorized products available	100%	0%	0%
GMP inspection report issued by local NRA in the past 3 years	89%	11%	0%
GMP inspection report issued by a competent regulatory authority in the past 3 years	83%	17%	0%
Recent annual product quality review conducted	96%	2%	2%
Batch manufacturing instruction, release procedure, and executed records	100%	0%	0%
Review of most recent complaints and any recalls due to product quality defect	75%	25%	0%

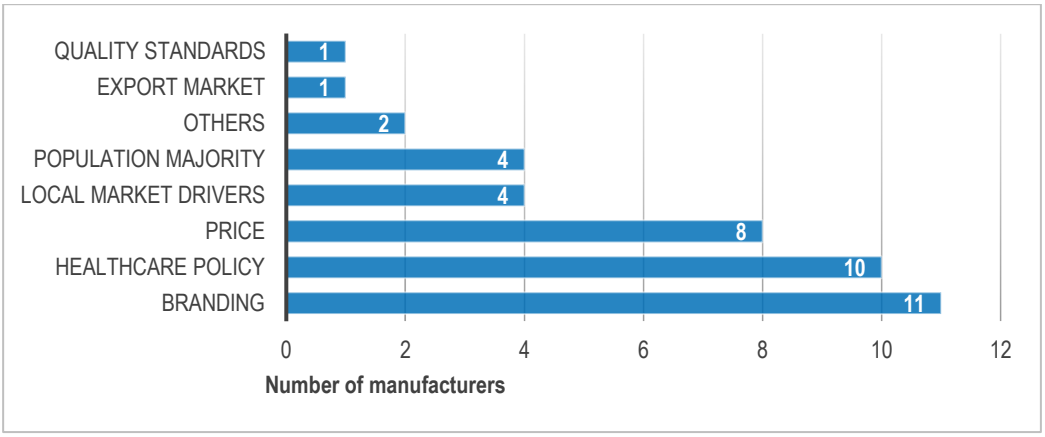
Approximately 90% of the manufacturers have developed processes for producing finished NTD products, while eight percent are beneficiaries of technology transfer. Two manufacturers were initially recipients of technology transfer and then used that information to develop their own in-house process. Regarding manufacturers' ability to scale up production in case of surges, only one third believed that they could meet the challenge and almost half believed they would be unable to do so (48.1%). The manufacturers identified technical challenges, supply of APIs, marketing factors, and regulatory challenges as key limitations to scale-up of production. Examples of these limitations are shown in Table 3.

Table 3. Challenges/Limitations to Scale-Up as Reported by Manufacturers

Factors Affecting NTD Manufacturing Scale-Up	Examples of Detailed Responses from Participating Manufacturers
Technical factors	• Unique characteristics of APIs (e.g., particle size, size distribution, polymorphism) makes production difficult. • Production line capacity and technical limitations
Marketing factors	• Low demand results in small market size. • Need to receive order before production • Profit margin is not attractive. • Importation of NTDs from several vendors (mostly from China) results in more competitive prices. • Shipment mode changes result in increased investment.
Supply of APIs	• Limited resources for APIs • Prices of APIs are not competitive, which has a direct impact on the price of FPPs.
Regulatory challenges	• The requirements for conducting bioavailability and bioequivalence studies are highly resource intensive. • API block list • Regulatory bindings, API importation approval • Current government restrictions on the price of azithromycin due to increasing demand for COVID-19 treatment

Manufacturers cited branding (i.e., market competition), healthcare policy (prioritization of NTD control by a country's government), and price as the top three market drivers for NTD products (Figure 3).

Figure 3. Key Market Drivers for the Market Leading Product of NTD Manufacturers



Discussion

Almost 80% of the surveyed manufacturers produce only one or two NTD products. Manufacturers in this region struggle with the development, manufacturing, and sales of more than one type of NTD medicine. For example, manufacturers reported that an average of 57% of their albendazole in stock and 67% of their ivermectin in stock were awaiting purchasers. Ideally, manufacturers do not hold stock and have 100% commitments for the procurement of products. If manufacturers focus strategically on products to meet regional demands, they may be able to reduce stock levels while producing a lower quantity of products.

There is potential for creating a supply chain/production network within a region through coordination of manufacturers, national regulatory agencies, and procurement agencies. Manufacturer stock awaiting a purchaser suggests that some countries (e.g., Thailand, Vietnam) may have the capacity to serve as regional production bases for NTD products, since their production capacity is adequate for both local and regional consumption. Lower income countries may find this type of regional network useful because it may not be feasible and economically viable to host their own independent manufacturers for NTD products. With ASEAN regulatory harmonization in place, a regional supply chain network should be explored to guide further actions and promote regional collaboration in the future.

A regional supply chain network would involve coordination among manufacturers of specific NTD products with the capacity to meet the demands of a network of member countries. Multiple manufacturers in the ASEAN region are unable to fill capacities with local demands alone. Unfilled production capacities result in low profitability for the already-low cost of NTD medicines. Low profitability risks facility closures, which can negatively impact access and countries' sustainability. The issue is exacerbated when multiple manufacturers produce the same products while being unable to reach full production capacity. A regional supply chain network could enable select manufacturers to focus on producing fewer/targeted NTD products based on the supply needs of the network while ensuring capacities are filled. This approach could assure efficiencies, profitability, growth, and overall sustainability of local access to NTDs.

- Among the seven NTD products assessed for availability in this report, praziquantel, diethylcarbamazine, and tetracycline eye ointment are most at risk of supply disruptions

due to a smaller number of manufacturers producing them relative to need. To address these concerns and protect the supply chains of these vulnerable items, specific actions should be considered:

- Technical support to improve understanding around the manufacturing of APIs that meet international quality standards
- Technical support—particularly in process control—to ensure that smaller manufacturers can meet regulatory requirements and standards at low cost
- Facilitation of partnerships between manufacturers and NRAs to create mutual understanding and collaboration (helping to sustain the supply of quality products)
- Intraregional collaboration and networks among countries to create a viable market size and demand

Although most manufacturers (77.4%) have received country market authorization for their registered NTD products, only 60% of the participating manufacturers fully met regulatory compliance items included in the survey. As more NRAs introduce and adopt updated standards and guidelines (e.g., GMP Pharmaceutical Inspection Co-operation Scheme [PIC/S]), a concern arises. Compliance with these evolving standards might necessitate increased research and development investments from manufacturers, potentially becoming mandatory for renewing the registration of these NTD products. Consequently, some manufacturers might face challenges in meeting these financial demands, ultimately impacting their ability to stay compliant and renew product registrations.

It is well known that LMICs have limited capacities to produce APIs. Data from this survey show a near complete dependence on India and China as the key sources of APIs for NTDs. Promotion of the production and use of NTD APIs from a wider range of countries in the Asia region should be considered. More than 90% of the manufacturers surveyed develop finished NTD product processes in-house.

Technical barriers exist beyond the ability to produce APIs. Only one third of the manufacturers reported that they could meet the challenge of scaling up the production of NTD products, citing “technical factors” as one of the most common challenges. As a result, technical support in various forms (e.g., product development and formulating) is needed to improve the capacity of these manufacturers and strengthen the supply of NTD products in this region.

The prevalence and incidence of NTDs are declining in general, largely because of mass drug administration using globally donated products. Meanwhile, Asian manufacturers struggle with having enough orders to fill the production capacity. Evidence from the landscape analysis shows the larger proportion of low production versus large-scale production of made-by-order batches produced of praziquantel, diethylcarbamazine, and tetracycline eye ointment manufacturing. Production on a made-by-order batch production indicates that manufacturers do not have consistent and large enough orders to produce these products continually. Conversely, larger stock inventory versus made-to-order batch levels of albendazole, mebendazole, ivermectin, and azithromycin were reported.

Hospitals, pharmacies, and government units are the primary purchasers of NTD products. Specific procurement arrangements vary from one NTD product to another. Results from this landscape analysis indicate that pharmacies and hospitals tend to be important channels of distribution of NTD products that are in higher demand, while government or NGOs are primary buyers for NTD products with limited usage. Results obtained from bulk procurement sources

showed that the private sector (66%) is the main distribution channel of these products with community pharmacies and private hospitals serving as the main channels.

The challenges of NTD manufacturing and quality assurance are multifaceted. For API supply, areas for improvement may include both the strength of supply and the quality of APIs. For manufacturing processes, most NTD products had been in the market for years before the introduction of current standards, which include GMP PIC/S, ASEAN Common Technical Dossier guidelines, WHO guidelines, and International Council for Harmonisation guidelines.[8] Meeting these new standards and guidelines will require manufacturers to install additional process controls and make significant investments. These are key obstacles that prevent compliance. Additionally, manufacturers and NRAs may both need training to create mutual understanding of today's standards.

Results: African Region

The data collected from the desk review led to the creation of a database consisting of 82 NTD product manufacturers based in Africa (Table 4), of which 67 are located in sub-Saharan Africa.

Table 4. Potential Manufacturers of NTD Products and Pharmaceutical Procurement Agents in Africa

Country	Number of Identified NTD Manufacturers	Number of Manufacturers that Responded	Number of Identified Procurement Agents	Procurement Agents that Responded
Nigeria	26	3	6	0
Kenya	10	3	6	0
Ghana	9	1	7	0
Egypt	8*	0	0	0
DRC	4	1	3	0
Tanzania	3	2	11	3
Ethiopia	3	0	10	0
Tunisia	3*	0	0	0
Algeria	3*	0	0	0
South Africa	2	0	0	0
Zambia	2	0	5	0
Malawi	2	0	4	0
Uganda	2	1	6	0
South Sudan	1	0	4	0
Morocco	1*	0	0	0
Ivory Coast	1	0	2	0
Namibia	1	0	4	0
Benin	1	1	2	0
Burundi	0	0	4	0
Rwanda	0	0	4	0
Mozambique	0	0	8	0
Liberia	0	0	1	0

[8] Nixon SA, Welz C, Woods DJ, Costa-Junior L, Zamanian M, Martin RJ. Where are all the anthelmintics? Challenges and opportunities on the path to new anthelmintics. Int J Parasitol Drugs Drug Resist 2020;14:8–16.

Country	Number of Identified NTD Manufacturers	Number of Manufacturers that Responded	Number of Identified Procurement Agents	Procurement Agents that Responded
Mali	0	0	3	1
Guinea	0	0	2	1
Total	**82**	**12**	**92**	**5**
*NTD drug manufacturers in Northern Africa				

Findings

Status of NTD products manufacturers surveyed

Twelve of the 13 manufacturing firms that responded to this survey are shown in Table 5.[9] Eleven of the responding firms produce one or more of the targeted NTD products. One company reported that it plans to start manufacturing NTD drugs, although its timeline was not clear.

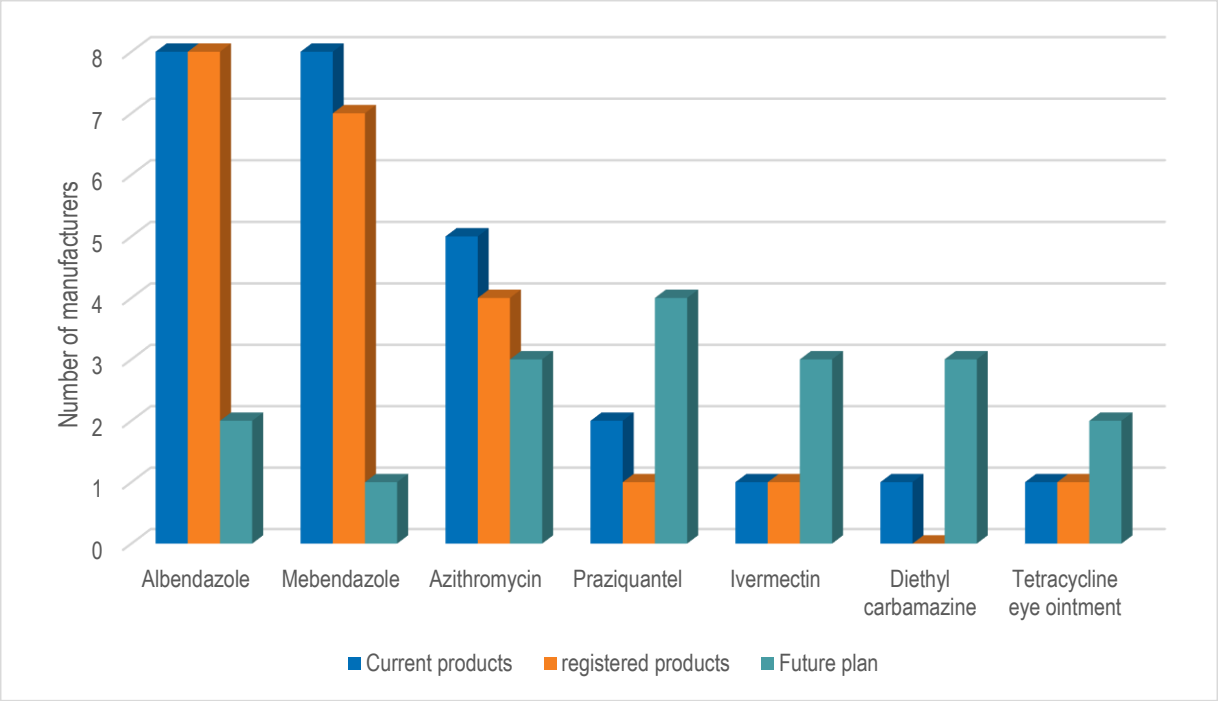
Table 5. African Manufacturers of NTD Products Surveyed

Code Name	Country	Targeted NTD Products Currently Manufacturing	Targeted NTD Products with Domestic Market Authorization	Future Plans for Manufacturing of Targeted NTD Products
Company 1	Benin	albendazole, azithromycin, diethylcarbamazine, mebendazole, praziquantel	albendazole, mebendazole	ivermectin, tetracycline eye ointment
Company 2	DRC	albendazole, azithromycin, mebendazole, tetracycline eye ointment	albendazole, azithromycin, mebendazole, tetracycline eye ointment	diethylcarbamazine, praziquantel
Company 3	Ghana	albendazole, azithromycin	albendazole, azithromycin	mebendazole
Company 4	Kenya	albendazole, mebendazole, praziquantel	albendazole, mebendazole, praziquantel	no
Company 5	Kenya	albendazole, azithromycin, mebendazole	albendazole, azithromycin, mebendazole	praziquantel, diethylcarbamazine, ivermectin
Company 6	Kenya	albendazole, azithromycin	albendazole	albendazole and praziquantel in development stage
Company 7	Nigeria	albendazole, ivermectin	albendazole	no
Company 8	Nigeria	albendazole, azithromycin, mebendazole	albendazole, azithromycin, mebendazole	diethylcarbamazine, ivermectin, praziquantel, tetracycline eye ointment
Company 9	Nigeria	albendazole, mebendazole		no
Company 11	Tanzania	mebendazole	mebendazole	azithromycin in registration
Company 12	Tanzania	no	not yet	azithromycin in development
Company 13	Uganda	mebendazole	mebendazole	albendazole, azithromycin

[9] The desk review indicated that Company 10 produced NTD drugs, and the company responded to the survey. Subsequently, the research team discovered that this manufacturer did not produce NTDs; therefore, it was removed from Table 5.

Figure 4 shows the distribution of the NTD medicines currently manufactured, registered with the local regulatory authority, and the companies' plans to produce NTD drugs.

Figure 4. NTD Drugs Regulatory Status



Albendazole, ivermectin, and tetracycline eye ointment produced by these firms have been registered by their NRAs. However, not all manufacturers of other drugs have all their products registered. Reasons for the lack of registration with the NRA are unknown. However, the lack of registration means a lack of regulatory oversight and uncertainty in the supply of quality mebendazole, azithromycin, praziquantel, and diethylcarbamazine by manufacturers within the affected markets.

Five pharmaceutical procurement agencies responded to the survey. The status of pharmaceutical procurement agents surveyed is shown in Table 6.

Table 6. Pharmaceutical Procurement Agents

Agency Name	Country	Agency Class	NTD Products Procured	Targeted NTD Products Received from Donations	Source of Procured Products	Type of Procurement or Receipt
Agency 1	Tanzania	Private	albendazole, azithromycin, mebendazole, praziquantel, tetracycline eye ointment		30% African industries	EML*, prime vendor to supply medicines to public facilities
Agency 2	Tanzania	Public	albendazole, azithromycin, ivermectin, praziquantel	All 7 products	0% African industries	EML, MDA*
Agency 3	Tanzania	Private	albendazole, azithromycin,		57% African industries	EML buys and sells medicines to its

Agency Name	Country	Agency Class	NTD Products Procured	Targeted NTD Products Received from Donations	Source of Procured Products	Type of Procurement or Receipt
			mebendazole, praziquantel, tetracycline eye ointment			customers without categorizing them as NTD.
Agency 4	Guinea	Public	albendazole, mebendazole, tetracycline eye ointment	albendazole, azithromycin, ivermectin, praziquantel tetracycline eye ointment,	0% African industries	EML, MDA
Agency 5	Mali	Public		ivermectin, praziquantel	0% African industries	EML, MDA program (donations only)

*EML= WHO Model List of Essential Medicines; MDA = mass drug administration
Note. *Private* agencies are owned solely by a private company (nongovernmental); *public* agencies are owned, or majority owned, by government.

As shown in Table 6, two of five responding pharmaceutical procurement agencies obtain NTD drugs through both direct procurement and donations. Only one agency (Agency 5) relies solely on donations. Depending on the demand, the five agencies procure or receive donations of NTD drugs differently, such as for EML and/or MDA. The type of NTD drugs (procured and/or donated) also differs between agencies, depending on the specific country's NTD profile.

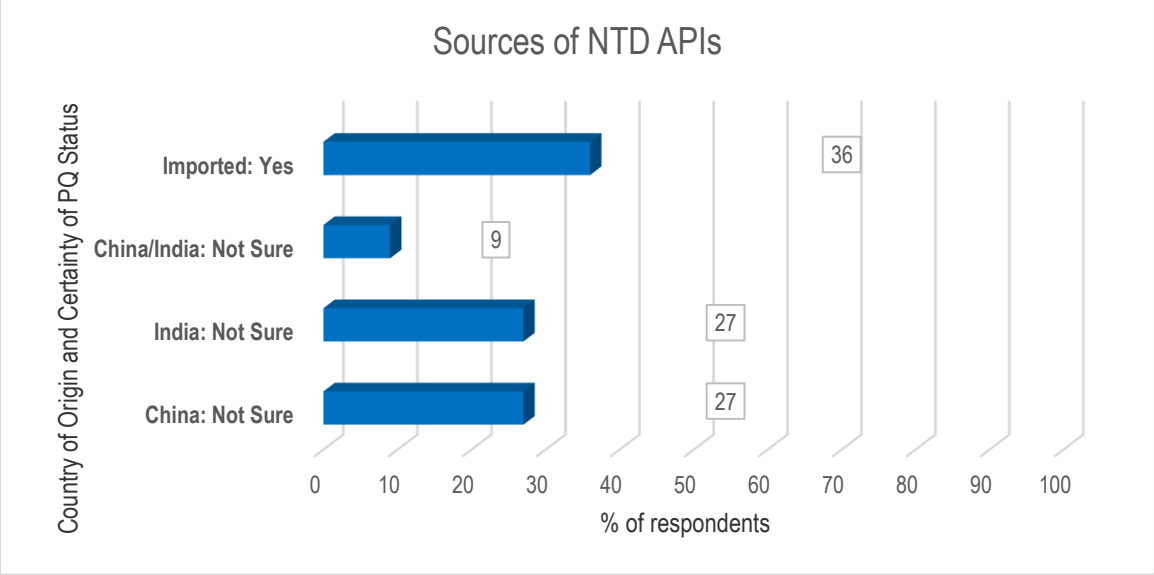
Notably, the manufacturers of NTD products received by the three public agencies are non-African. The two private agencies rely more on local African manufacturers versus non-African manufacturers to source NTD products (up to 57%). Procurement of locally manufactured NTD products by private agencies supports their sustainability. The responses reveal an opportunity for public agencies to begin procuring products from African manufacturers.

GMP certification status—that is, those qualified to answer the question about GMP certification for NTD products manufacturing—are GMP certified as follows: 10 (91%) by their NRA and one by WHO. GMP certifications indicate that the manufacturer meets the minimum qualifications to manufacture products in accordance with GMP standards.

Sources of NTD APIs

All NTD products manufacturers that responded are involved in secondary manufacturing, producing FPPs by importing their APIs. Only seven of the 11 firms (64%) stated their APIs' country of origin (China and India). Most (63%) of these seven were uncertain whether the APIs are WHO prequalified and were unable to ascertain the quality of their APIs. The remaining four companies (36%) did not state the APIs' country of origin, but they reported that the APIs are WHO prequalified, indicating that they are confident in their quality (Figure 5). Knowing the source and quality of APIs is critical in assuring the safety, quality, and efficacy of FPPs.

Figure 5. Origin of APIs and Respondents' Certainty of PQ Status



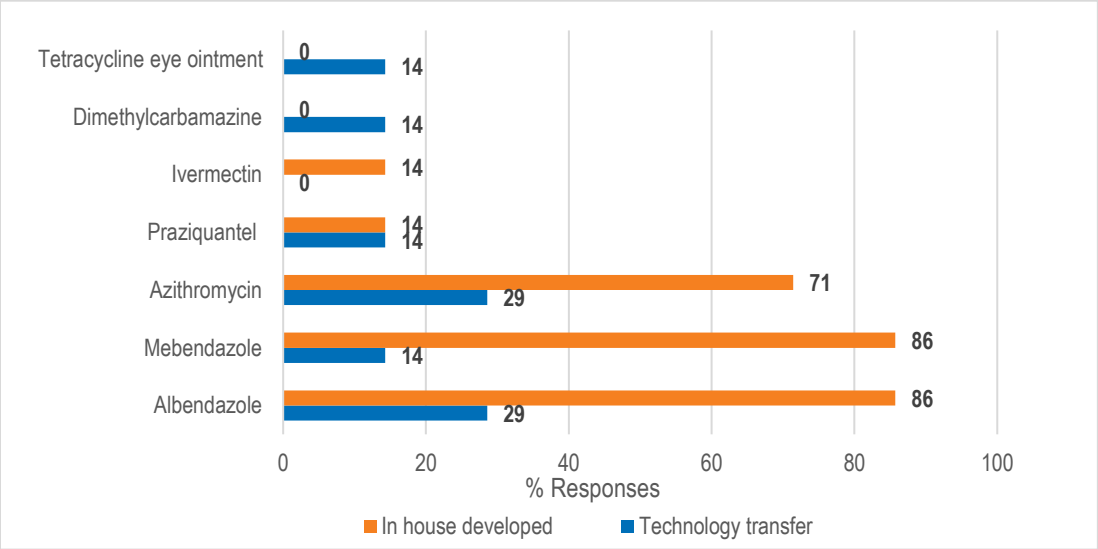
Technical capabilities of the NTD manufacturers

The FPP formula

All responding manufacturers formulate and package NTD FPPs. Of the manufacturers surveyed, six companies (86%) have developed formulations in-house for their NTD products, while one company depends solely on technology transfer from an India-based manufacturer (Figure 6). Two companies have developed some processes in-house and rely on technology transfer for other products.

The prevalence of in-house formulations suggests that manufacturers have in-house expertise and are self-reliant for the development for NTD products. This proficiency suggests that these manufacturers possess internal capabilities that enable self-reliance in formulation. The use of technology transfer can streamline product development timelines and is particularly beneficial for manufacturers equipped with proficient formulators. Manufacturers with internal expertise not only demonstrate self-reliance but also exhibit enhanced capability in formulating other related products.

Figure 6. Source of the Formulation Used in FPP



Annual production capacity

The responding firms indicated their installed capacity (i.e., the maximum amount of product that the manufacturer is capable of producing) versus demand (utilized capacity—how much product is actually produced for customers). Eight manufacturers provided information on their production capacity. Capacities vary greatly between manufacturer and product. The one manufacturer in Benin has a significantly larger capacity than all others for all products. Its capacity is 800, 50,000, 4,000, and 4,000 times that of lowest volume producers of albendazole, azithromycin, mebendazole, and praziquantel, respectively. Only one manufacturer is reported for diethylcarbamazine and ivermectin (Table 7). Data provided by 27% of the companies are insufficient to determine utilization rates, current production capacities, and possibilities to expand production. In many cases, the reluctance to divulge these data was due to confidentiality concerns.

Table 7. Annual Production Capacity of the Manufacturing Companies

NTD Product	Company Location(s)	Annual Production Capacity (Tablets)
Albendazole	Benin	1,000,000,000
	Ghana	20,000,000
	Kenya	1,200,000
	Kenya	100,000,000
	Nigeria	87,000,000
	Nigeria	20,000,000
Azithromycin	Benin	1,000,000,000
	Ghana	5,000,000
	Kenya	20,000
	Kenya	300,000
	Nigeria	24,000,000
Diethyl carbamazine	Benin	200,000,000
Ivermectin	Nigeria	115,000,000
Mebendazole	Benin	2,000,000,000

NTD Product	Company Location(s)	Annual Production Capacity (Tablets)
	Nigeria	6,000,000
	Tanzania	100,000,000
	Kenya	600,000
	Kenya	500,000
	Nigeria	20,000,000
Praziquantel	Benin	200,000,000
	Kenya	50,000
Note. Table 7 displays the total capacity of each reporting manufacturer in that country (i.e., private and public) of the indicated medicine. Note that in some countries, several companies manufacture NTD medicines; each is listed separately.		

Production and marketing challenges for NTD products

The research team assessed the capacity of selected NTD pharmaceutical manufacturing firms and identified the major challenges they face to increase or maximize production. The production and scale-up problems reported include the following:

- Delivery time of APIs and equipment
- Lack of major equipment
- Technical challenges with quality control
- Market dynamics and capacity
- Pricing issues
- Low demand due to importation of cheap brands from Asian countries
- Availability of quality packaging materials, technical knowledge about maintaining production equipment, and stocking spare parts
- Competition with imports

Regulatory and policy challenges

The responding firms are required to have market authorization for their products, ensuring continued compliance with applicable laws and regulations. However, lead time on NRA registration for market authorization varies from country to country. Only 40% of the companies (all located in Benin, Democratic Republic of the Congo [DRC], and Nigeria) reported that they have an undefined “short” lead time. Manufacturers in Ghana, Kenya, Tanzania, and Uganda reported a “long” lead time. Longer lead times inhibit the flexibility of national supply chains, can lead to disruptions in availability of quality-assured medical products, and must be considered when planning for procurements.

Lead time for overseas procurement of FPPs can be substantial. For example, one company indicated a period of 12 months between order placement and the arrival of products. This may lead to stock-outs and wastage of products (by reducing shelf life of certain commodities) as well as scarce financial resources.

All responding firms reported government financial support, which can ease a manufacturer’s burden. However, government incentives (land, access to loans, and taxes) vary from country to country. About 40% of all companies receive incentives from their governments. Other companies (i.e., those in Ghana, Nigeria, Uganda = 60%) do not receive any incentives. One company in Kenya receives incentives, but other companies from the same country do not. Respondents offered no explanation for why this is so.

In addition to challenges associated with NTD drug market dynamics, an obstacle to manufacturing affordable and quality products appears to be the cost of production and access to modern technologies. Lack of major equipment for production, equipment failure, availability of spare parts, availability of packaging materials, and lack of capacity affects the production yield in these companies.

Regulatory compliance

GMPs ensure that products are consistently produced to the quality standards appropriate for their intended use as required by the regulatory authority.[10] Of the 11 GMP certifications received by NTD drug producing firms, 10 were from their national drug authorities. Only one company obtained GMP certification from WHO. A limited number of manufacturers in sub-Saharan African countries have WHO GMP-compliant manufacturing plants. Based on the survey findings, only 27% of the companies surveyed have been assessed by SRAs. The impact of SRA assessments is explained on page 4 of this document.

Cost of production

The small scale of most sub-Saharan African NTD drugs manufacturers tends to increase the unit costs of production. This is because most sub-Saharan African manufacturers rely on imported sources for most of their required APIs, excipients, primary packaging materials, machinery, and equipment. Import duties and value-added taxes on raw materials needed to produce these products locally increase the final product costs. Importing inexpensive products from countries like India and China disincentivizes manufacturers from manufacturing products with high raw materials import duties and taxes.

Market access

Thirty-six percent of manufacturers reported challenges with market access, including NTD drugs market dynamics and competition with cheap imports. The market share of local NTD drug production is low, and supply systems often favor imports for reasons noted earlier in this document. While donors supply a significant share of the NTD medicines consumed in sub-Saharan African countries, some procurements are performed through international competitive bidding and are normally restricted to NTD manufacturers with WHO prequalification (PQ). Because local NTD drug manufacturers in Africa are not WHO prequalified, they cannot compete for procurements where PQ is required. However, some local manufacturers are eligible for tenders where WHO PQ is not required. Providing technical assistance to sub-Saharan African manufacturers that leads to WHO PQ could expand access by qualifying local manufacturers to compete for international procurements.

Recommendations

Recommendations for NTD product manufacturing and procurement in Asia

The results of this survey suggest that the ASEAN and South Asia region has opportunities to build capabilities in API product development, improve GMP compliance, and coordinate among countries to improve access to quality NTD products.

[10] World Health Organization. Health products policy and standards. https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/guidelines/production.

- **Building capacity for self-reliance:** While 90% of manufacturers in the ASEAN and South Asia region develop finished products internally, manufacturing APIs is a challenge. Manufacturers noted that the supply of APIs, market factors, and regulatory challenges are key limitations to the production scale-up needed for self-reliance. Currently, imported FPPs from China are more competitively priced than locally produced FPPs. APIs, the costliest component in FPPs, are also mostly imported. Locally produced APIs can enable more competitively priced FPPs and self-reliance. There are also regulatory hurdles associated with importing FPPs and APIs. These regulatory issues can be circumvented by local API manufacturing. Manufacturers can start by gaining the necessary knowledge on NTD API manufacturing and fostering technology transfers. Similarly, NRAs and national quality control laboratories must build competencies in APIs, as they are responsible for regulating and testing, respectively.
- **Improving regulatory compliance and quality:** Building manufacturing capacity alone will not assure patients of quality, safe, and efficacious products, since only 60% of manufacturers participating in this survey comply with GMP regulations. A mechanism to become GMP compliant and ensure NTD product quality is needed for manufacturers to achieve WHO PQ. Many of the manufacturers in the region existed prior to the introduction of GMP, PIC/S, and WHO PQ standards and may benefit from, for example, technical support and training, to become compliant.

- **Regional mobilization to protect the local market for local NTD pharmaceutical manufacturers:** Results of the PQM+ program's analysis suggest that several countries (e.g., Thailand, Vietnam) may have the capacity to serve as a production base for most NTD products for countries in the region. Coordination between governments and manufacturers may be especially beneficial for lower income countries that cannot independently afford to produce and fulfill the demands for NTD products for their citizens.

Recommendations for NTD product manufacturing and procurement in sub-Saharan Africa

The findings in this report suggest that there is a need for a strategy to develop the value chains of NTD products. The absence of local production of APIs on the continent has a strong impact on prices and availability of locally manufactured NTD products. Localizing the production of APIs for NTD drugs may improve access to these medicines at more affordable prices.

- **Regional mobilization to protect the local market for local NTD pharmaceutical manufacturers:** One of the key objectives of the African Union is to create a regional market for goods and services produced by member states. As is the case with many other categories of goods, this objective is yet to be fully achieved for pharmaceuticals. There is fierce competition in the regional market created by cheap generic medicines from China, India, and Pakistan. Across the region, pharmaceutical producers cannot compete with Asian producers on pricing. African member states should consider taking concerted measures to protect regional pharmaceutical production and procurement. For example, governments can offer favorable taxation to promote local manufacturing while increasing taxes on imports from manufacturers outside of the region.

- **Implementation of government incentives:** Sixty percent of the survey respondents indicated that an incentive structure for producing NTD products is not in place. Governments should expand the range of incentives offered for local pharmaceutical

production (e.g., grants and other financial incentives, public-private partnerships, purchase guarantees, and capacity-building support).

- **Strengthen regulation of the pharmaceutical sector:** Ratification of the African Medicines Agency will be an important step toward harmonizing regulatory guidelines to tackle the challenge of assuring quality through coordinated NTD drug manufacturing monitoring. The African Medicines Agency will be a key stakeholder in promoting a harmonized set of standards and regulatory policies for pharmaceutical product manufacturers, including for NTDs. Supporting selected manufacturers to achieve WHO PQ, SRA or ML3 or higher NRA may allow these manufacturers to participate in international bids for large volume orders for MDA. Having more WHO-prequalified manufacturers also supports reliance within the African Medicines Agency, whereby manufacturer information is shared among member NRAs.

There are similarities between supply deficiencies within the ASEAN/South Asian and African regions. Both regions have ample manufacturing capacity that is not fully utilized. Many manufacturers operate on a small batch production model, fulfilling customer orders without sufficient demand to maintain stocked products. Countries without any production capacity or capability could benefit from manufacturers in the region with ample capacity to ensure access to critical medicines. Of the Asian manufacturers surveyed, 57% produce more than one NTD product while having underutilized capacity. Similarly, in Africa, 82% of manufacturers produce two or more NTD products.

To optimize their manufacturing capacity, these firms may need to concentrate on medicines most in demand. Coordination between governments would enable the determination of what the volume demands are by product and determining where medicines are most efficiently produced based on manufacturer capacity, regulatory compliance, logistical considerations, and other factors to ensure access.

An impediment to growth of NTD products manufacturing in Africa and Asia is their lack of regulatory compliance with international GMP standards. Achieving international standards not only opens avenues for manufacturers to enter other markets but also increases orders, leading to sustainability. However, merely improving GMP standing among manufacturers is not sufficient; regulatory agencies must also mature to ensure effective compliance oversight. Therefore, a comprehensive approach involving regulatory system strengthening alongside improvements in manufacturer compliance is necessary. Technical support for both NTD product manufacturers and regulators is crucial to overcoming these challenges.