WHO Prequalification

Building quality-assured manufacturing capacity in Nigeria

As a fast growing economy and large provider of goods and services to countries in the region, Nigeria is poised to expand its pharmaceutical production to achieve self-sufficiency in essential medicines and compete on regional and global markets. To this end, government health authorities and local manufacturers requested WHO support and technical assistance to prequalify several locally produced medicines, as a way to fast-track the building of local capacity to manufacture medicines according to international quality standards. An integral part of the process is the strengthening of national regulatory capacity to enforce these standards on an ongoing basis.

The Nigerian quest
While no medicines manufacturer in West Africa has so far achieved prequalification of a pharmaceutical product by the World Health Organization (WHO), Nigeria is attempting to change the status quo. A number of companies belonging to the Pharmaceutical Manufacturers Group of the Manufacturers Association of Nigeria (PMG-MAN) are working to reach a manufacturing quality standard that will enable them to have some of their products WHO-prequalified and apply for international medicines tenders.

The project has been supported by the Nigerian government and by the National Agency for Food and Drug Administration (NAFDAC). WHO was approached to provide technical assistance to both manufacturers and regulators especially in the areas of good manufacturing practice and dossier submissions in line with WHO and international standards.

Role of WHO
The WHO prequalification programme aims to ensure that medicines for priority diseases meet global standards of quality, safety and efficacy. By evaluating needed pharmaceutical products – including those produced in countries with limited regulatory capacity – the WHO prequalification team (WHO/PQT) provides a basis for national and international procurers to make cost-effective choices among finished products of assured quality.

WHO/PQT has increasingly engaged in activities that go beyond dossier assessment and site inspections. The team is training national regulators, providing guidance to manufacturers, facilitating registration in countries and supporting post-procurement quality control. The experts who advise manufacturers in preparing prequalification submissions work independently of the prequalification dossier assessment and inspection groups. The main objective of these activities is to disseminate sound knowledge and practices and to ensure that all the actors work together according
to the same international quality standards.

From the WHO perspective, the Nigerian project is in line with these aims. Given the importance of Nigeria in its geo-economic region, it is hoped that increased production of quality medicines in the country will also lead to better quality medicines in West Africa as a whole.

**Snapshot of Nigeria’s pharmaceutical landscape**

Nigeria is a natural candidate for the local capacity strengthening offered by WHO/P QT. The country’s pharmaceutical industry is vibrant and expanding, with over 100 pharmaceutical manufacturers and a mostly local ownership organized under the umbrella of the Pharmaceutical Manufacturers Group of the Manufacturers Association of Nigeria (PMG-MAN). Nigeria accounts for approximately 60% of the pharmaceutical production in the Economic Community of West African States (ECOWAS) by volume (1). Production is geared mostly towards essential medicines, including antimalarials and HIV medicines.

On the other hand, drug manufacturers in Nigeria face a number of constraints. These include a weak financial base, high production costs as a result of the high cost of imported pharmaceutical ingredients and machinery, infrastructural problems, outdated technology and weak distribution systems. In addition, as there are no contract research organizations in West Africa proven to work in line with international standards, manufacturers need to rely on expertise from Europe and Asia when they require bioequivalence studies or specific laboratory testing. Due to these factors, the country imports about 70% of its medicines, mainly from Asia, Europe and the Americas.

In terms of the regulatory environment, the National Agency for Food and Drug Administration and Control (NAFDAC) has in recent years enacted numerous enforcement activities to combat substandard and counterfeit medicines. It has also consistently worked with WHO to strengthen its quality control and post-marketing monitoring of pharmaceuticals. But challenges persist, which are largely related to insufficient capacity to ensure full regulatory functions in line with international standards, including speedy registration of medicines.

Despite these challenges, the country’s pharmaceutical sector is one of the strongest in Africa in terms of size, range of products manufactured and potential to meet and sustain international pharmaceutical quality standards.

**The project**

**Selection of manufacturers**

In 2011 NAFDAC and WHO/P QT came to an agreement on the principles of the project and, in collaboration with PMG-MAN, selected eight manufacturers that had expressed commitment to invest in quality improvements and that were deemed technically ready to embark on a programme to align their manufacturing operations with international quality standards. WHO/P QT arranged for external experts to verify the production standards at the manufacturing sites and to assess product data and documentation.

**Capacity-building**

Based on the results of the assessments by the external experts, WHO/P QT initiated an intensive capacity-building programme for Nigerian manufacturers.
and regulators. Since 2012, several training sessions on good manufacturing practices, combined with site visits at participating companies, have been co-organized by WHO/PQT and NAFDAC. In parallel, WHO-appointed experts have advised the companies on specific quality issues related to various medicines.

In response to observations raised during the audits and document reviews, the companies implemented a series of corrective actions. They upgraded their equipment, improved manufacturing processes, and established professional procedures to build documentation for pharmaceutical ingredients and finished products. These corrective actions exceed currently applicable regulatory requirements in Nigeria. Implementation is monitored by NAFDAC professionals, who report on progress to WHO. The process is ongoing, with a current focus on the development of technically sound product dossiers.

WHO/PQT also works with the participating manufacturers to identify all their medicinal products eligible for prequalification. This will facilitate progress towards GMP-compliant production of additional medicines of interest for international organizations. For example, interest may come from UN Commission for Lifesaving Commodities for Women and Children (UNCoLSC), given that a large portion of the medicines needed in the West African region are reproductive health and paediatric products.

Regulatory and in-country support
On the regulatory side, NAFDAC has proved to be a strong partner in capacity-building efforts. The authority has upgraded its laboratories, recruited more specialized staff and has established new departments, such as the Clinical Trial/Pharmacovigilance and Post Marketing Surveillance and Drug Evaluation and Research Directorates. NAFDAC professionals also participate actively in trainings organized for local industry.

The close support by the WHO Country Office has also been an asset to the project. The process has opened doors for Nigerian stakeholders and international organizations to work together more closely.

Pre-submission audits
The WHO prequalification team normally plans its inspections on a risk-basis once companies have submitted a prequalification dossiers. To enable applicants to work on product dossiers and good manufacturing practice (GMP) in parallel, the new concept of pre-submission GMP audits was piloted in Nigeria. An inspection can be scheduled before a dossier has been submitted, provided that the expert advisors and NAFDAC notify WHO/PQT that the manufacturer has achieved – in principle – compliance with WHO GMP. Prequalification inspectors then verify the status of general GMP compliance while completion of a prequalification dossier is still ongoing.

Successful audits represent a milestone in the progress towards prequalification, and the outcomes are considered by organizations looking for companies that manufacture needed health products in line with international GMP.

A series of pre-audits was organized in 2013 and 2014 at Nigerian manufacturing sites in close co-operation with NAFDAC, whose regulatory inspectors played an active role in verifying the corrective actions adopted after the audit and drafting parts of the inspection reports.
Funding
The Nigerian Ministry of Health has invested considerably into the project. In addition, advocacy is on-going for a special intervention fund from the development banks in Nigeria, ECOWAS and the African Development Bank (AfDB).
WHO’s participation in the project has largely depended on financial backing from UNITAID, which was used to support technical assistance, transfer of knowledge, capacity building, audits and inspections and human resources.
From the manufacturers’ side, information from PMG-MAN indicates that the companies participating in the project have invested a cumulative amount exceeding USD 400 million over the last four years.

Achievements
GMP compliance
The pre-submission audits led to a landmark success being achieved in April 2014, when Swiss Pharma Nigeria Limited (Swipha) was confirmed to be operating at an acceptable level of compliance with WHO GMP guidelines for the manufacture of oral solid dosage forms (2). Swipha was the first pharmaceutical manufacturer in Sub-Saharan West Africa to pass a GMP inspection by WHO/PQT after implementing successful corrective and preventative action (CAPA). Three other companies participating in the project - Evans Medical Plc, May & Baker Nigeria Plc and CHI Pharmaceuticals Ltd – reached this standard in November 2014, after successfully implementing corrective and preventive action (CAPA) identified during WHO pre-submission audits in May 2014 (3).

Prequalification dossiers
One Nigerian company has submitted a prequalification dossier to WHO and this has been accepted for screening. Another submission is expected before the end of the year, with more to follow in the near future. The choice of medicines includes antimalarials, antiretrovirals, zinc sulphate and antibiotics.

Outlook and impact
Tenders
The achievements made by participating manufacturers open up opportunities for international tenders, where compliance with stringent GMP is a minimum requirement for any pharmaceutical product. Additional requirements apply to key categories such as antiretrovirals, anti-TB products and antimalarials. In these categories, compliance with stringent GMP enables manufacturers to apply for review of relevant products by the Expert Review Panel (ERP). Products that have received a positive ERP opinion can then compete in international tenders in situations where no or only one WHO-prequalified or stringently authorized competitor product is available on the market (4).

It is hoped that African ministries of health, regional initiatives and international procurers will consider WHO GMP-compliant African manufacturers in tenders for purchase of medicines in the region. This would support quality-assured local production, and would signal recognition of the cost that quality assurance entails for manufacturers.

Raising the bar for medicines quality
Feedback from PMG-MAN suggests that the project is beginning to yield wider benefits. The understanding of world class manufacturing practices in
Nigeria has improved. As a result, the perception of the importance of quality in pharmaceutical manufacturing is gradually shifting. Other Nigerian companies do not want to be left behind and are also becoming interested in upgrading their production, with support from PMG-MAN, to achieve WHO prequalification of their products.

NAFDAC has benefitted through hands-on participation in prequalification inspections, assessments, training workshops and other capacity-building activities, with access to prequalification inspection and assessment reports.

Local regulatory oversight
Medicines regulation is essentially a public function that should be assured by the governments of countries where medicines are produced and used. NAFDAC’s active follow-up of individual manufacturers’ progress and verification of corrective actions has proved extremely valuable in working towards this goal. The process has strengthened communication between industry and regulators, with a common understanding of the quality issues at stake.

The cooperation with NAFDAC under this project marks the start of a new model whereby the local regulatory authority assumes responsibility for ensuring that WHO prequalification requirements continue to be met. This approach is of course dependent on objective evidence that the local regulatory authority can in fact conduct routine monitoring and maintenance to the required standards. The activities will therefore be coordinated with, and reported to, WHO/PQT. In addition, NAFDAC assessors will work closely with the WHO prequalification assessors to review product dossiers submitted by Nigerian companies in line with international standards.

Challenges
Further challenges lie ahead before the Nigerian pharmaceutical sector will be able to reach the level of quality production and autonomy to which it aspires. Most challenges are related to the need for further guidance in manufacturing practices, dossier development, bio-equivalence and supply chain management. To address these needs, the initial timeline for the project was extended.

Important also is the choice of products for prequalification, which must be well considered to ensure that it serves both quality and commercial objectives.

Other challenges are related to financing. Given the fact that WHO prequalification will not occur immediately, financial incentives may well be needed for the companies to continue to progress. And while WHO prequalification of a number of Nigerian-made products in the near future seems feasible and can enable companies to win international procurement tenders, further change is needed to ensure a sustainable supply of quality medicines in the region and to resolve supply management problems.

Conclusion
The close cooperation between Nigerian manufacturers, regulators and WHO starts to produce results. The general understanding of international regulatory standards has improved, and several companies are well on their way towards prequalification of their products.

As corrective measures and upgrades continue, Nigerian authorities and manufacturers will need to find ways to raise sufficient funds to put into place
sustainable structures and processes for production of quality-assured pharmaceuticals.

Spokespersons of NAFDAC and PMG-MAN have expressed satisfaction with progress made to date and remain firmly committed to enhancing the pharmaceutical sector to make it work both for public health and the pharmaceutical industry.

WHO will continue to advocate for greater support of this kind of cross-sectoral capacity-building. Ensuring that affordable, quality-assured medicines are within reach of all those who need them is a pillar of an effective health system and an area requiring greater attention from the international community.

References

1 Nigeria pharmaceutical country profile. Published by Federal Ministry of Health in collaboration with the World Health Organization. June 2011.

2 WHO/PQT. First Nigerian manufacturer considered compliant with WHO GMP. Prequalification Update, 4 April 2014.
