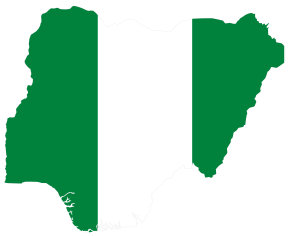

NIGERIA
GMP ROADMAP

A stepwise approach for the pharmaceutical industry to attain internationally recognised GMP standards

Produced as part of an ECOWAS regional initiative

DRAFT

NIGERIA GMP ROADMAP

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2019

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This GMP Roadmap is the product of a collaboration between the National Agency for Food and Drug Administration and Control (NAFDAC), the Pharmaceutical Manufacturers Group of Manufacturers Association of Nigeria (PMG- MAN) and the United Nations Industrial Development Organisation (UNIDO) Support has been provided by the West African Health Organisation (WAHO) as part of its work to develop the pharmaceutical sector in the ECOWAS region. It has been made possible by the leadership of Professor Moji Christianah Adeyeye, the Director General of NAFDAC and strong engagement by the Executive Board of PMG-MAN.

The document has been produced by Kay Weyer, Lead GMP Expert, under the overall guidance of Alastair West, PMPA Business Plan Coordinator. Uche Sonny-Afoekelu (UNIDO National Expert, Nigeria, seconded from NAFDAC) has managed the project and provided substantial contributions for the development of this document. Technical inputs have been provided by Alain Kupferman, Arie Maat and Ibelema Emeh.

Ms Ijeoma Nwankwo (Director, Drug Evaluation and Research Directorate) has acted as the Focal Point for NAFDAC, and has been integrally involved throughout the project. The Executive Board of PMG-MAN has also been heavily involved in driving the process which, along with the voluntary involvement of many of its members, has been central to enabling this project to be conducted and this output achieved.

The document forms part of an ongoing collaboration between WAHO and the United Nations Industrial Development Organization (UNIDO) to develop a strategy for region-wide upgrading of the pharmaceutical industry across West Africa. The current phase of the program is funded by WAHO.

DRAFT

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LIST OF ABBREVIATIONS

AfDB	African Development Bank
CAPA	Corrective and Preventive Action Plan*
CDA	Compressed Dried Air
ECOWAS	Economic Community of West African States
ERPP	ECOWAS Regional Pharmaceutical Plan
FPP	Finished Pharmaceutical Product
GMP	Good Manufacturing Practice
HVAC	Heating, Ventilation and Air Conditioning
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
NAFDAC	National Agency for Food and Drug Administration and Control
OOS	Out Of Specification
OOT	Out Of Trend
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PMGMAN	Pharmaceutical Manufacturers Group Manufacturers Association of Nigeria
PMPA	Pharmaceutical Manufacturing Plan for Africa
PSN	Pharmaceutical Society of Nigeria
QMS	Quality Management System
SOP	Standard Operating Procedure
TRS	Technical Report Series
UNIDO	United Nations Industrial Development Organization
USP	United States Pharmacopeia
WAHO	West African Health Organization
WHO	World Health Organization

I. INTRODUCTION

This document presents a Good Manufacturing Practice (GMP) Roadmap for the Nigerian pharmaceutical manufacturing industry. It has been developed as part of a collaboration with National Agency for Food and Drug Administration and Control (NAFDAC) and the Pharmaceutical Manufacturing Group Manufacturers Association of Nigeria (PMGMAN) to establish the basis for strengthening the country's pharmaceutical industry to enable all manufacturers to reach internationally recognised standards of GMP. This GMP roadmap approach was presented to stakeholders including senior representatives from NAFDAC, PMGMAN, the Federal Ministry of Health, United States Pharmacopeia (USP) and others at a validation workshop in April 2019, where it received endorsement from those present.

Nigeria is the most populous country in Africa with over 200 million people and has the largest pharmaceutical manufacturing sector on the continent with at least 150 active manufacturers, of which over 100 are members of the PMGMAN.

The pharmaceutical market is regulated by NAFDAC, which since its inception 25 years ago has made significant strides to, inter alia, reduce the amount of falsified products in circulation and increase the quality of products on the market. It has supported the development of four manufacturers to achieve international GMP standards, as recognised by the World Health Organization, and continues to make progress in reducing the level of falsified products in the market, whilst also striving for increased levels of quality for products to receive marketing approval. NAFDAC has also implemented policies in support of the local pharmaceutical such as the five plus five registration validity policy that is explicitly designed to support "migration to local production". Strengthening the national pharmaceutical industry is also a focus for the Pharmaceutical Society of Nigeria, which back in 2005 set a target for the country to produce at least 70% of the pharmaceuticals that the country requires.

Hence there are a number of strong institutions that are striving to both reduce the prevalence of substandard and falsified medicines and to increase the proportion of national needs that can be sourced from local manufacturers. Despite the progress that has been made, Nigeria is estimated to rely on imports for 70% of its pharmaceutical needs and substandard and falsified products still pose a significant threat to public health. The ongoing reliance on imports is evidenced by data from India which places Nigeria as the 5th largest export market for Indian pharmaceutical products, estimating that in the six months from April to October 2018, pharmaceutical exports to Nigeria were $256m[1]

Alongside the national level progress and ongoing activities, the ambition to strengthen the pharmaceutical industry in Africa has been articulated by leaders at Regional Economic Community and continental levels, not least through the African Union's Pharmaceutical Manufacturing Plan for Africa (PMPA) and the West African Health Organization's ECOWAS Regional Pharmaceutical Plan (ERPP). These and other initiatives recognise that improved access to safe, effective, affordable medicines can be increased through strengthening of the industry; by increasing the levels of quality assurance, facilitating enhanced regulatory oversight for products on the market (due not least to proximity of production) and through expanding the range of medicines that are produced. These

[1] Source: India Brand Equity Foundation: https://www.ibef.org/exports/pharmaceutical-exports-from-india.aspx

developments could also drive an increase in trade within the region and the continent as well as to other parts of the world.

However, developing the pharmaceutical industry is a long term undertaking that requires a multifaceted approach to address the challenges that manufacturers and associated stakeholders face. Ultimately, establishing and maintaining high standards of manufacturing requires many issues to be addressed in a coordinated fashion given, for example, the need for affordable financing to invest in this capital intensive business. It also requires highly skilled human resources that have expertise in the industrial application of multiple disciplines (across technical, operational and commercial dimensions). Strong regulatory oversight is required to prevent falsified medicines from eroding the market, and access to export markets and the international donor funded markets are further potential sources of revenue that require and can support sustainable manufacturing at internationally recognised standards. Access to technology, such as through voluntary licensing, foreign direct investment and other mechanisms would help address the need to expand the range of products that are produced in Nigeria and could be an important component in reducing the reliance on imports as well as increasing exports.

Therefore ambitions to develop the pharmaceutical industry in Africa have been established, and as the country with the largest sector on the continent, Nigeria has a number of key attributes and strong institutional activists and advocates for furthering this objective.

Another aspect that needs to be considered is time. It takes time to upgrade plants or build new facilities, it takes time to implement robust quality management systems and it takes time to build on established academic credentials to develop expertise in industrial application of these skills.

Importantly, this GMP roadmap provides a central component to developing the industry. It focuses on the technical aspects of pharmaceutical manufacturing and adherence to GMP. Compliance to internationally recognised GMP involves a vast array of issues to be addressed across all aspects of manufacturing and these cannot be achieved overnight. Furthermore, to those less familiar with the specifics, the entirety of these requirements can be daunting and may appear unachievable. However, without addressing the majority of the issues covered by the standard referenced in this document, namely WHO GMP, significant risks to production safety are inevitable.

This document is based on the United Nations Industrial Development Organization's (UNIDO) methodology for developing a national level GMP roadmap. It involves establishing a baseline of the range of current manufacturing practices and levels of compliance to GMP as implemented by industry incumbents. This is done through utilising experienced international GMP experts to assess a representative sample of manufacturers. The results from these assessments are then analysed and the key technical challenges that pose most threat to production safety are prioritised in a stepwise, risk based approach for upgrading the industry. It provides guidance to industry and regulators on milestones that should be targeted to satisfy specific detailed aspects of GMP. Furthermore, its implementation enables companies to put in place measures that mitigate risks to production safety through development and application of corrections and corrective action (CAPA) plans. To ensure that manufacturers are making the requisite progress in implementing these company level plans the developments at a site level can be monitored by NAFDAC.

This roadmap is focused on the strengthening of the pharmaceutical industry in Nigeria. It has been developed as part of a regional initiative by the West African Health Organization in collaboration

with UNIDO to develop a Regional GMP Framework to facilitate aligned progress in standards of pharmaceutical manufacturing across the ECOWAS region. Establishing the technical baseline of the range of compliance with internationally recognised GMP and establishing a framework for improving standards, including a common methodology for assessment and monitoring of compliance levels, provides the basis from which programmes to address the hurdles that face stakeholders at the national and regional level (as described above) can be developed and implemented. Thus, upgrading of the industry in Nigeria can be overseen by NAFDAC, implemented by PMGMAN, its members and other registered manufacturers, and enabled through coordinated approaches to address bottlenecks facing the industry through a comprehensive pharmaceutical industrial development programme. Such a programme will require inputs from multiple partners at the national level. Regional and international dimensions will also have a significant contribution to make.

II. THE NIGERIA ROADMAP TOWARDS WHO GMP

1 Overarching considerations for developing of this Roadmap

Adherence internationally recognised Good Manufacturing Practice (GMP) is essential to ensure quality, safety and efficacy of medicinal products. However, due to limited financial, technical and human resource capacities, pharmaceutical manufacturers of finished products in Nigeria are often overwhelmed by the vast array of GMP requirements, making it difficult for them to operate in line with requisite standards.

As part of the implementation of the ECOWAS Regional Pharmaceutical Plan (ERPP) and in order to support Nigerian manufacturers of finished pharmaceutical products (FPP) in their progress towards GMP compliance, a Roadmap has been developed that delineates a phased approach with clearly defined requirements and milestones to be achieved over a specified period of time. In line with the regional framework, WHO GMP has been identified as the reference for this roadmap for a number of reasons including:

- that it involves standards that are accepted widely across the world
- that achieving these is a prerequisite for accessing the donor funded markets.

The Roadmap development has been tailored to the specific situation in Nigeria and built on a baseline assessment of Nigerian pharmaceutical manufacturers in terms of their level of compliance with WHO GMP. In this context, a tool for risk categorisation of FPP manufacturers, according to their compliance with WHO GMP was developed.

The resulting Nigeria GMP Roadmap should be used as a stepwise tool to guide FPP manufacturers on the path towards WHO GMP compliance and to support NAFDAC to monitor and evaluate progress at the plant level. Manufacturers that are currently operating can use the Roadmap together with the risk assessment in order to perform a gap analysis between their current manufacturing practices and WHO GMP requirements, and to follow a stepwise approach towards WHO GMP compliance. Over and above the volunteer companies that were assessed to develop this roadmap (see section 4 below), NAFDAC has conducted assessments of all other manufacturers that are active in Nigeria utilising the methodology outlined in this document with support from the United States Pharmacopeia (USP). In conjunction with this roadmap, these assessments can provide a technical basis for developing the Corrections and Corrective Action plans required for each manufacturer to move from their current status to internationally recognised GMP in a stepwise manner that meets agreed milestones and to implement immediate risk mitigation measures where necessary. Moderation of the results from the different assessment initiatives would be required to ensure compatibility between the two.

Furthermore, this Roadmap and the technical annex can be used by new start-up companies to assure that all necessary elements and systems are taken into consideration, and that they are in place before the actual launch of the company. The Roadmap also enables NAFDAC to review licensing criteria for new and existing facilities in order to ensure alignment with WHO GMP requirements.

2 Objectives

Given that a pathway towards compliance with WHO GMP tailored to the specific situation in Nigeria was to be developed, the following activities were performed:

- Definition of key aspects and tools for the development of the Nigeria GMP Roadmap.
- Baseline assessment of existing manufacturing practices in the Nigerian pharmaceutical industry, in order to evaluate the level of compliance with WHO GMP across the range of FPP manufacturers in Nigeria, and also to identify the main technical challenges faced by these pharmaceutical manufacturers.
- Development of a GMP Roadmap reflecting the outcomes of the baseline assessment. In order to develop a scientifically sound and achievable approach towards implementation of WHO GMP, the Nigeria GMP Roadmap needed to delineate a risk-based, phased approach towards compliance with WHO GMP tailored to the specific situation in the country.

3 Scope

The scope of this document includes in line with the ERPP:

- Manufacturers of finished pharmaceutical products (FPP) for human use which manufacture
    - Medicinal products containing small molecular active ingredients, that are active substances with a molecular weight of not more than 800 g/mol
    - Sterile and non-sterile dosage forms

The scope excludes:

- Manufacturers of finished pharmaceutical products (FPP) for human use which manufacture medicinal products containing large molecular active ingredients, i.e. biopharmaceuticals
- Manufacturers of finished pharmaceutical products (FPP) for veterinary products
- Pharmaceutical manufacturers other than manufacturers of finished pharmaceutical products (FPP) such as distributors, importers, wholesalers, raw materials manufacturers, packaging material manufacturers

4 Baseline assessment of existing manufacturing practices in the Nigerian pharmaceutical industry

As a starting point for developing the Nigeria GMP Roadmap, the baseline of the current manufacturing practices over a representative cross-section of FPP manufacturers in Nigeria needed to be established, and the main technical challenges identified. Therefore, assessments of the level of compliance with WHO GMP of a sample of pharmaceutical manufacturers in Nigeria were performed.

4.1. Approach

The following approach was used for the baseline assessment of existing manufacturing practices in the Nigerian pharmaceutical industry:

1. Development of tools for assessment of Nigerian pharmaceutical manufacturers and their evaluation regarding compliance with WHO GMP
2. Criteria for selection of FPP manufacturers for assessment
3. Assessments of selected FPP manufacturers
4. Evaluation of results gathered during assessments

4.2. Development of tools for assessment of Nigerian pharmaceutical manufacturers and their evaluation regarding compliance with WHO GMP

The focus of the baseline assessment was on manufacturers with different levels of compliance to WHO GMP, but which were aiming to achieve full compliance, and which were representing the landscape of FPP manufacturers in Nigeria. Hence, several pharmaceutical manufacturers had to be assessed using unified procedures, and the results gathered had to be evaluated using unified criteria. Therefore, before the baseline assessment was conducted, unified tools had to be developed to allow for a transparent assessment of the participating manufacturers. This methodological groundwork comprised the following activities:

- Selection of a GMP reference standard for assessment of FPP manufacturers
- Definition of key elements and focus areas during assessments
- Preparation of an assessment schedule
- Selection of a rating scheme for the observations
- Development of tools for the evaluation of assessment results

4.2.1. GMP reference standard for assessment of FPP manufacturers

The internationally recognized GMP standard used as reference for the assessment of pharmaceutical manufacturers in Nigeria was the GMP standard as outlined by the World Health Organization (WHO) in the document *"Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2, 2nd updated edition. Good manufacturing practices and inspection. World Health Organization, Geneva, 2007"*, as subsequently updated through the WHO Technical Report Series (TRS), especially TRS 986, Annex 2.

WHO GMP provides a unified standard based on the principles and practices agreed by the world's leading regulatory agencies, and hence receives wide international acceptance. Additionally, many pharmaceutical manufacturers in Nigeria strive to achieve compliance with WHO GMP, since this forms part of the requirements for having their products prequalified by WHO.

4.2.2. Key quality elements, focus areas during assessment and assessment schedule

The assessment was based on seventeen key quality elements of WHO GMP:

1. Pharmaceutical Quality System
2. Utilities impacting Good Manufacturing Practice (GMP)
3. Sanitation and hygiene
4. Qualification and validation

5. Complaints
6. Product recalls
7. Contract production, analysis and other activities
8. Self-inspection, quality audits and suppliers' audits and approval
9. Personnel
10. Training
11. Personal hygiene
12. Premises
13. Equipment
14. Materials
15. Documentation
16. Good practices in production
17. Good practices in quality control

Each of the key quality elements were divided into sub-sections for which the assessment focus had been defined. Through this detailed planning, it was possible to ensure that the same standards and criteria were applied for all pharmaceutical manufacturers assessed. The document outlining the sub-sections and the focus of assessment for each of the above mentioned key quality elements can be found in Appendix I.

Based on the defined key quality elements and focus areas of the assessment, an assessment schedule was prepared and uniformly applied for all FPP manufacturers involved. Each manufacturer was assessed for two full days. The assessment schedule is displayed in Appendix II.

4.2.3. Rating of observations

Observed deficiencies were rated based on the compilation of EU community procedures on inspections and exchange of information (London, 3 October 2014, EMA/572454/2014 Rev 17). The assessments were performed during 2018 and 2019, and the deficiencies were classified as follows:

Critical Deficiency:

A deficiency which has produced, or leads to a significant risk of producing a product which is harmful to the patient.

Major Deficiency:

A non-critical deficiency,

which has produced or may produce a product, which does not comply with its marketing authorisation;

or

which indicates a major deviation from Good Manufacturing Practice;

or

which indicates a major deviation from the terms of the manufacturing authorisation;

or

which indicates a failure to carry out satisfactory procedures for release of batches or a failure of the Authorized Person to fulfil his/her legal duties;

or

a combination of several "other" deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such.

Other Deficiency:

A deficiency, which cannot be classified as either "critical" or "major", but which indicates a departure from Good Manufacturing Practice. (A deficiency may be "other" either because it is judged as minor, or because there is insufficient information to classify it as major or critical.)

4.2.4. Tools for evaluation of assessment results

In order to evaluate the level of compliance of Nigerian pharmaceutical manufacturers with WHO GMP, and to identify the main technical challenges across the range of pharmaceutical manufacturers in Nigeria, two tools were developed:

Tool 1: Identification of the key quality elements with highest and lowest WHO GMP compliance,

Tool 2: Categorization of FPP manufacturers based on their compliance with WHO GMP

Tool 1: Identification of key quality elements with highest and lowest WHO GMP compliance, respectively

A tool needed to be developed to compare WHO GMP compliance between FPP manufacturers, and to identify those key quality elements to which highest and lowest compliance was observed. Using the plain ratings of individual observations made during assessment of each manufacturer would not have been suitable due to the variety of individual observations. Therefore, based on severity of observations made during the assessments, a rating of the compliance of key quality elements with WHO GMP was derived. A key was developed which made it possible to provide an overall rating for each of the key quality elements reflecting the range of observation related to a specific key quality element. Key quality elements were rated using the following key:

- **Acceptable**: Compliance of a key quality element with WHO GMP was rated "acceptable" if no or only "other" (i.e. "minor") deficiencies were observed in areas related to this specific key quality element.
- **Improve**: Compliance of a key quality element with WHO GMP was rated "requires improvement" (short: "improve") if only a few (≤ 5) "major" deficiencies were observed in areas related to this specific key quality element.
- **Inadequate**: Compliance of a key quality element with WHO GMP was rated "inadequate" if at least one "critical" and/or a considerable number (> 5) of "major" deficiencies were observed in areas related to this specific key quality element, or if the entire quality element was not available at a pharmaceutical manufacturer.

This rating key fulfilled the aforementioned requirement to compare performances of FPP manufacturers, and to identify those key quality elements to which highest and lowest compliance were observed. Hence, the main technical challenges for compliance could be identified. The rating key is a useful tool to evaluate particular weaknesses in compliance identified for local pharmaceutical manufacturers.

The described evaluation tool can also be used for trending of GMP compliance of FPP manufacturers, and for monitoring their development towards full WHO GMP compliance throughout the implementation of the GMP Roadmap.

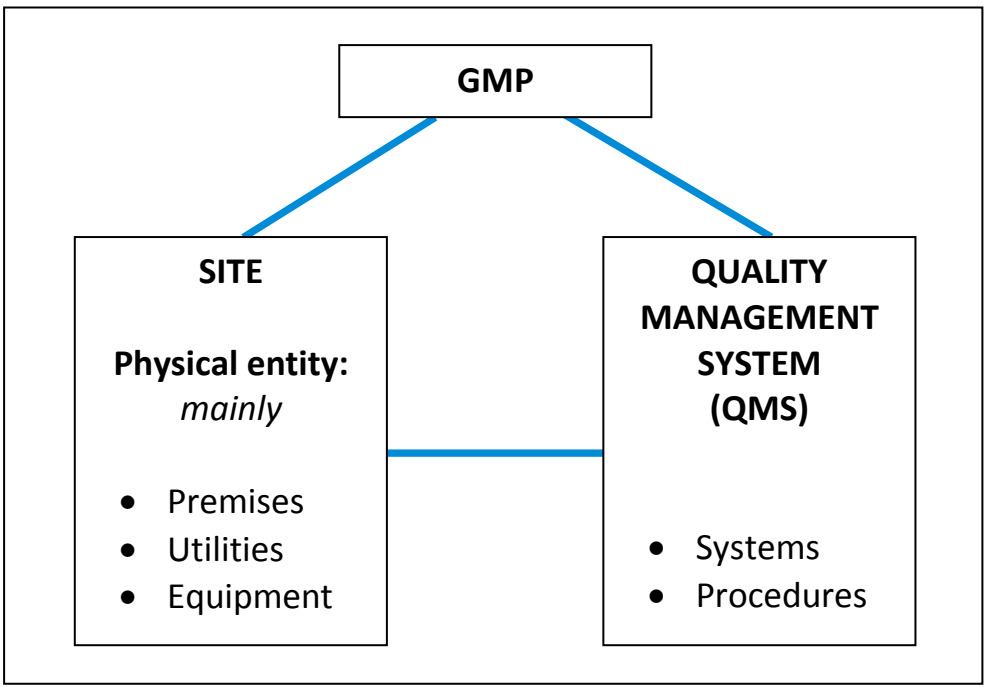
Tool 2: Categorization of FPP manufacturers based on their compliance with WHO GMP

GMP compliance encompasses the implementation and adherence to a vast array of requirements. Depending on the financial, technical and human resource capacities available, the level of GMP compliance varies significantly between pharmaceutical manufacturers in Nigeria. The spectrum ranges from FPP manufacturers that are relatively close to achieving WHO GMP compliance, to those that have multiple critical issues to address.

The significant range in adherence to GMP compliance by pharmaceutical manufacturers required the development of a tool for categorization of the compliance risk associated to the pharmaceutical manufacturers under assessment.

GMP compliance can be understood as the result of adherence to requirements of both structural and organizational measures. In this document the term “site” is used for the physical entity of mainly premises, utilities and equipment applied for pharmaceutical manufacturing. The term “quality management system” (QMS) is used for all documentation systems and procedures applied by a pharmaceutical manufacturer to ensure GMP compliance. The interconnection between site, QMS and GMP is illustrated in figure 1.

Figure 1: Interconnection between Site, QMS and GMP.



The tool uses a matrix to categorize FPP manufacturers based on the two risk-indicating factors for GMP compliance:

- Compliance of site with WHO GMP standards, and
- Compliance of quality management systems with WHO GMP standards.

Figure 2: Matrix for categorization of pharmaceutical manufacturers based on their GMP compliance

		Quality Management Systems (QMS)		
		3 No QMS in place	**2** Requirements are implemented sporadically only; a systematic approach to GMP is not in place	**1** A systematic approach in line with WHO GMP in place and implemented
Site	**1** Site is in general compliant with WHO GMP	**C**	**B**	**A**
	2 Site shows significant deficiencies from WHO GMP, but does not impair production safety	**C**	**B**	**B**
	3 Site unsuitable for pharmaceutical manufacturing → production safety impaired	**C**	**C**	**C**

A	Existing approach towards pharmaceutical manufacturing in general in line with WHO GMP requirements	→	**low risk manufacturer**
B	Existing approach towards pharmaceutical manufacturing not in line with WHO GMP but reduced risk with regards to production safety	→	**medium risk manufacturer**
C	Existing approach towards pharmaceutical manufacturing not in line with WHO GMP and high risk with regards to production safety	→	**high risk manufacturer**

The term “risk” in this document is used solely in a technical context, and relates to a systematic, technical approach to evaluate and improve the effectiveness of risk management, control and governance processes in connection with the GMP-related assessment of pharmaceutical manufacturers. The term “risk” is therefore utilized in reference to Good Manufacturing Practice, and

is an accepted technical term recognized by international regulatory bodies including WHO as well as other organizations such as the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S).

Three risk levels were assigned to both site and quality management system to describe their compliance with WHO GMP, with level "3" representing a high compliance risk, and level "1" representing a low compliance risk.

A matrix, shown in Table 1 above, was provided for combining these two risk levels in order to generate an estimate of the compliance risk associated with a pharmaceutical manufacturer. The resulting risk ratings were "A", "B" and "C". A rating of "C" indicates high risk manufacturers with non-compliance to WHO GMP, even causing a high risk to production safety. A rating of "A" indicates low-risk FPP manufacturers, where the existing approach towards pharmaceutical manufacturing is, in general, in line with WHO GMP requirements.

In order to increase transparency of the scores given for the compliance of site and QMS with WHO GMP, indicator criteria were defined. The guidance for the score criteria is presented in Appendix III.

This risk categorization is a suitable tool for benchmarking GMP compliance of FPP manufacturers, and can also be used in conjunction with tool 1 (detailed above) to monitor the manufacturers' development towards full WHO GMP compliance.

4.3. Criteria for selection of FPP manufacturers for assessment

According to information provided by NAFDAC over 180 FPP manufacturers were licensed and operational in Nigeria (2017). In order to ensure that the FPP manufacturers selected for the baseline assessment reflected the entire pharmaceutical manufacturing landscape of Nigeria several selection criteria were defined. The participation of manufacturers in this baseline assessment was on a voluntary basis.

The selection criteria for inclusion of pharmaceutical manufacturers in the assessment were:

a) Pharmaceutical manufacturers within the scope of this document having not yet achieved full compliance with WHO GMP; i.e. manufacturers which have not yet been found WHO GMP complaint after an inspection by the WHO inspection team

b) Pharmaceutical manufacturers representing different levels of GMP compliance across the pharmaceutical manufacturing sector

c) Pharmaceutical manufacturers from different geo-political zones, covering at least the geo-political zones with the highest pharmaceutical manufacturing activity, i.e. South West Zone (SWZ), South East Zone (SEZ) and North Central Zone (NCZ)

d) Pharmaceutical manufacturers of non-sterile as well as sterile dosage forms

e) Pharmaceutical manufacturers of medicinal products considered essential for the Nigerian market as determined by NAFDAC

f) Pharmaceutical manufacturers willing to participate in the assessment.

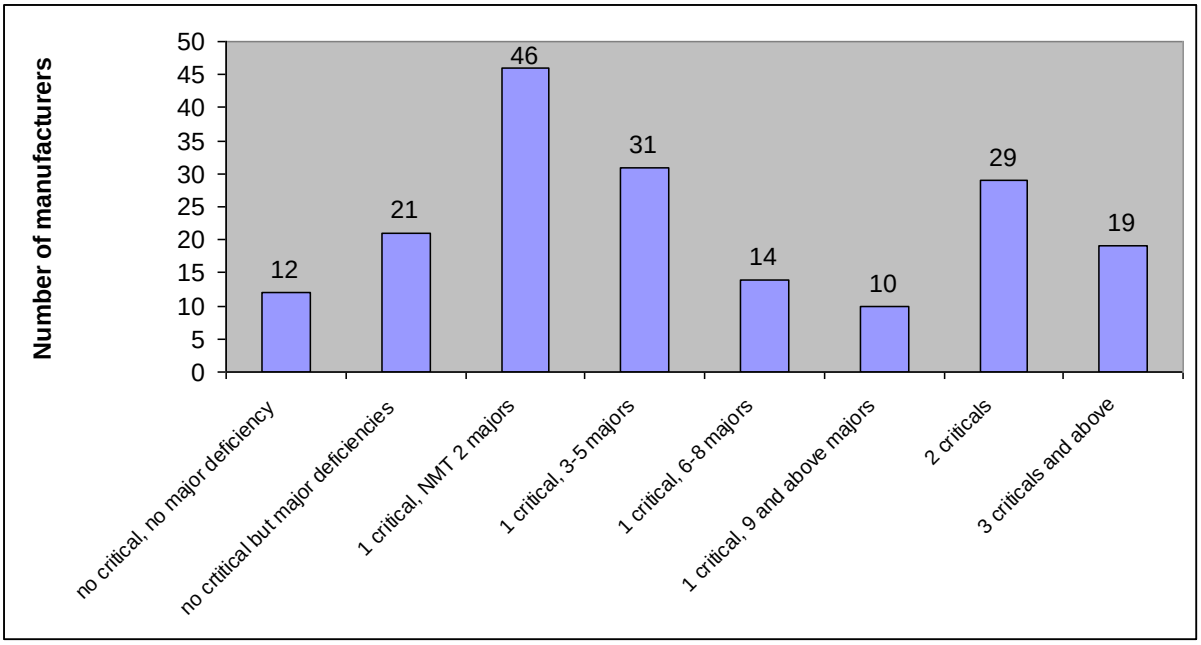
Whereas information for criteria a), c), d), e) and f) was available, a means to identify the level of GMP compliance was not directly available. Hence a methodology based on the outcome of the most recent (at the time) GMP assessment by NAFDAC was developed to ensure the baseline assessment represented the range of GMP compliance levels to which Nigerian manufacturers adhere.

Pharmaceutical manufacturers of finished pharmaceutical products for human use were divided into classes regarding their GMP compliance based on their performance during their last inspection by NAFDAC. Inspection data was provided by NAFDAC for a total of 182 pharmaceutical manufacturers. The classification was done taking into consideration number and severity of GMP non-compliances observed during the last inspection. Based on the data provided eight classes were created as follows:

- Class 1: FPP Manufacturers for which no critical and no major deficiencies had been observed during the last NAFDAC inspection
- Class 2: FPP Manufacturers for which no critical but major deficiencies had been observed during the last NAFDAC inspection
- Class 3: FPP Manufacturers for which one (1) critical but not more than two (2) major deficiencies had been observed during the last NAFDAC inspection
- Class 4: FPP Manufacturers for which one (1) critical and three (3) to five (5) major deficiencies had been observed during the last NAFDAC inspection
- Class 5: FPP Manufacturers for which one (1) critical and six (6) to eight (8) major deficiencies had been observed during the last NAFDAC inspection
- Class 6: FPP Manufacturers for which one (1) critical and nine (9) and above major deficiencies had been observed during the last NAFDAC inspection
- Class 7: FPP Manufacturers for which two (2) critical deficiencies had been observed during the last NAFDAC inspection
- Class 8: FPP Manufacturers for which three (3) and above critical deficiencies had been observed during the last NAFDAC inspection

The resulting histogram is shown in figure 3.

Figure 3: Histogram showing the distribution of Nigerian FPP manufacturers as per the classes created



FPP manufacturers for the baseline assessment were selected from various classes in order to ensure that the sample taken represented different levels of GMP compliance across the pharmaceutical manufacturing sector.

4.4. Assessment results and evaluation

The baseline assessments were conducted in 2017 and 2018. Assessment results of 25 Nigerian FPP manufacturers were utilized for development of this GMP roadmap. 25 volunteer manufacturers were identified through support from PMG-MAN and NAFDAC, such that the sample met the requirements outlined in section 4.3. The sample assessed therefore included:

- Pharmaceutical manufacturers within the scope of the project (see section 3).
- None of the pharmaceutical manufacturers previously been found to be GMP complaint after an inspection by a WHO inspection team.
- FPP manufacturers representing different levels of GMP compliance across the pharmaceutical manufacturing sector. In fact FPP manufacturers from all classes except class 6 were included in the baseline assessment. This represented an adequate cross section of the different levels of GMP compliance across the pharmaceutical manufacturing sector.
- Pharmaceutical manufacturers representing different geo-political zones, covering the geo-political zones with the highest pharmaceutical manufacturing activity, i.e. South West Zone (SWZ), South East Zone (SEZ) and North Central Zone (NCZ).
- FPP manufacturers including manufacturers of non-sterile products as well as manufacturers of sterile products. Out of the 25 FPP manufacturers 18 manufactured non -sterile products only, 3 manufactured sterile products only and 4 manufactured sterile and non-sterile products.
- Pharmaceutical manufacturers of medicinal products considered essential for the Nigerian market as determined by NAFDAC. Out of the 25 FPP manufacturers assessed, 3 manufactured medicinal products considered essential for the Nigerian market. (Note:

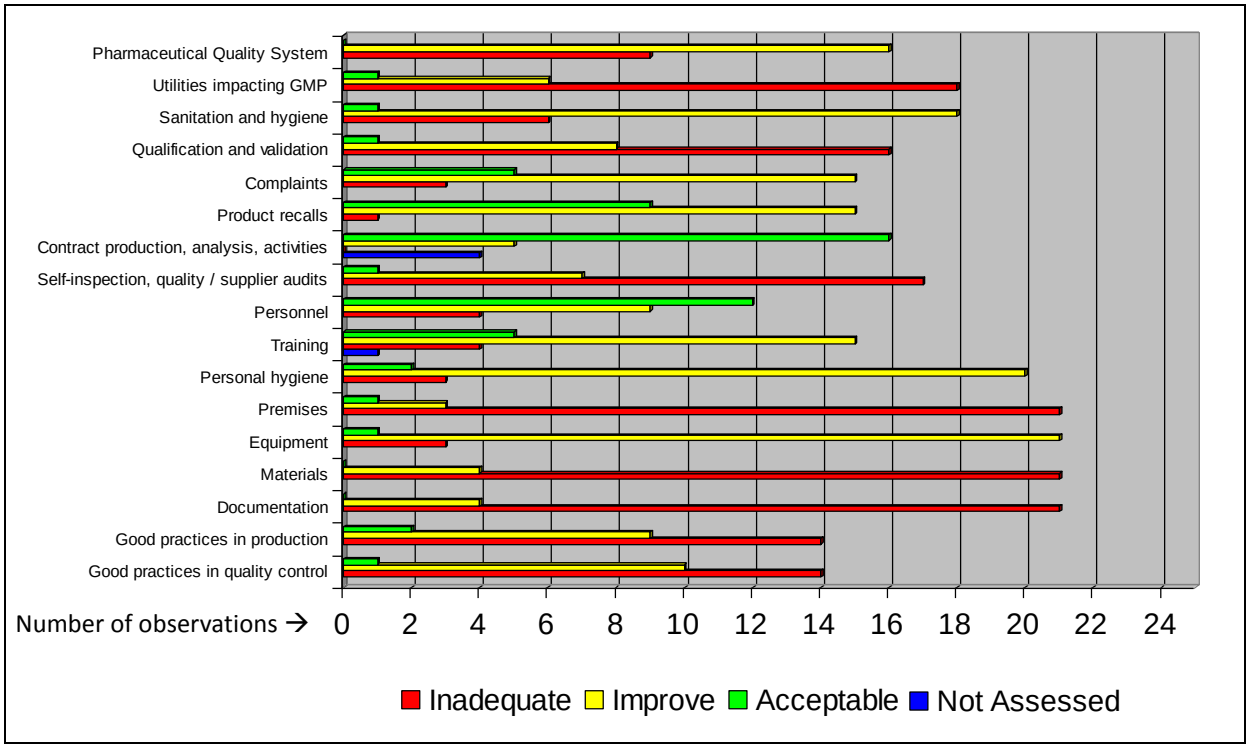
According to information provided by NAFDAC, only six Nigerian pharmaceutical companies manufacture products considered to be essential to the Nigerian market based on their limited availability.)

The results gathered during the assessments have been anonymized. No company names or details which would allow tracing of participants are presented.

4.4.1. Compliance of participating FPP manufacturers to key quality elements of WHO GMP

The results regarding compliance of participating FPP manufacturers to key quality elements of WHO GMP are shown in figure 4.

Figure 4: Overview of compliance of participating FPP manufacturers to individual key quality elements of GMP



The results above show that compliance with WHO GMP of a substantial majority of key quality elements need improvement or were inadequate. Although pharmaceutical manufacturers participating in the assessment were very interested in upgrading their GMP compliance, the number and severity of observations indicated that there is a need to increase awareness of WHO GMP requirements within the pharmaceutical industry (and to take action to enable companies to take the requisite steps to address short falls). It also indicates that ongoing training of NAFDAC inspectors should continue, to further increase capacity when it comes to identifying actions that should be taken with regard to GMP compliance, to attain or maintain a manufacturing licence. At least one NAFDAC inspector (up to three in some cases) participated in each of the assessments alongside a recognised international expert. They were also involved in writing up and signing off of the assessment reports. This process in itself is reported to have been beneficial to the inspectors that have participated. Such hands on transfer of knowledge could be considered as a valuable component of the implementation of this GMP roadmap given that further opportunities for

assessment, reassessment and CAPA monitoring in conjunction with international experts would likely be part of the process.

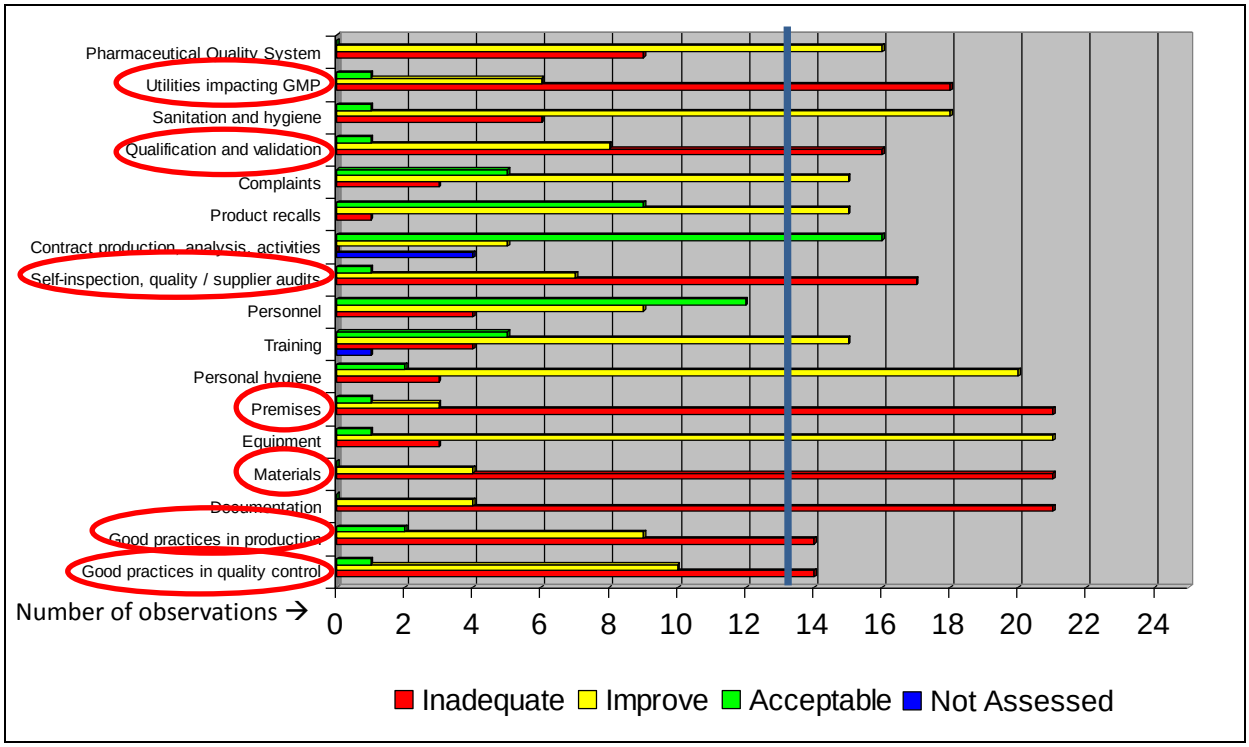
Despite the high number of quality elements which were either rated “inadequate” or “improve” for most of the manufacturers, the scientific degrees held by personnel was, for the majority of manufacturers, adequate. Nevertheless, despite the fact that personnel in general held adequate scientific degrees the graphic shows that personnel knowledge, awareness and behaviour caused serious GMP deficiencies at several manufacturers. This observation is reflected in the rating for the key quality element “Personnel”. The discrepancy between the adequate scientific degrees of personnel on the one hand and the inadequate practices on the other potentially reflects a generalised problem. It implies that the application of academic training in the industrial setting needs to improved, perhaps through increased inclusion of industrial modules in curricula and continued post qualification training.

The other key quality element for which the majority of manufacturers showed adequate compliance was “Contract production, analysis and other activities”. The reason for this adequate compliance is the fact that only few manufacturers outsource production and analytical activities. For the majority of manufacturers outsourcing of activities was limited to pest control and calibration services for which in general no serious deficiencies regarding the outsourcing process was observed. However, where production or analytical activities were outsourced, major deficiencies regarding the outsourcing process were frequently observed.

Figure 5 highlights the key quality elements for which the majority of FPP manufacturers showed inadequate compliance. These are:

- Utilities impacting Good Manufacturing Practice (GMP)
- Qualification and validation
- Selfinspection, quality / supplier audits
- Premises
- Materials
- Documentation
- Good practices in production
- Good practices in quality control

Figure 5: Identification of the Key quality elements that need to be prioritised based on analysis of the level of compliance level analysis



The most prevalent deficiencies causing "inadequate" ratings for the above mentioned key quality elements are summarized in table 2.

Table 2: Overview of typical deficiencies resulting in inadequate compliance of the key quality elements for which manufacturers showed least compliance

Key Quality Element	Typical deficiencies resulting in "inadequate" ratings
Utilities impacting Good Manufacturing Practice (GMP)	Inadequate utilities coming into direct product contact leading to a risk of (cross-)contamination (ventilation and water systems but also compressed air and steam systems)
Qualification and validation	Absence of qualification and validation activities
Self-inspection, quality / supplier audits	Absence of qualification of manufacturers of raw materials
Premises	Inadequate premises not allowing for realization of a zone concept and not allowing for adequate cleanability; inadequate separation of operations, flow of materials and space leading to mix-ups and (cross-)contamination; absence of pest control measures
Materials	Fumigation for pest control not only in warehousing areas but even production areas

	using organophosphates with no or inadequate mitigation of contamination risks; use of materials of inadequate quality (e.g. technical grade, reagent grade) for pharmaceutical manufacturing; inadequate sampling and dispensing practices; inadequate warehousing practices leading to deterioration, contamination or mix-ups; inadequate rework practices
Documentation	Several data integrity issues; no control of documentation system; documentation practices not allowing for traceability of materials and products; absence of documentation of process steps
Good practices in production	Practices leading to (cross-)contamination, mix-ups or lack of sterility of products; absence or inadequacy of in-process controls
Good practices in quality control	Absence of material and product testing; absence of stability testing; no or inadequate handling of OOS results including testing into compliance; falsification of data; lack of reference standards

The assessments allowed the identification of a total of eight key quality elements that are least implemented in Nigeria, and hence are of high priority for improvement with a view to ensuring quality, safety and efficacy of the manufactured products.

4.4.2. Results of categorization of FPP manufacturers based on their compliance with WHO GMP

FPP manufacturers participating in the assessment have been risk categorized using tool 2 as described in section 4.2.4. The risk categorization was based on the WHO GMP compliance of two risk-indicating factors, namely site and quality management systems.

The results of the risk categorization of FPP manufacturers based on their compliance with WHO GMP are shown in table 3.

Table 3: Results of categorization of FPP manufacturers based on their compliance with WHO GMP

Risk level Site	Risk level QMS	Overall GMP rating	Number of FPP manufacturers	Total number of FPP

			with these ratings	manufacturers with same "Overall GMP ratings"
1	1	A	0	0
1	2	B	2	11.5
2	1	B	1	
2	2	B	8.5*	
2	3	C	0	13.5
3	2	C	10.5*	
3	3	C	3	

*One manufacturer obtained different compliance ratings for the manufacture of different dosage forms assessed which is reflected by assigning the number "0.5" to the two respective ratings

The categorization shows that none out of the 25 FPP manufacturers assessed obtained an "A" rating which means that none of the manufacturers was considered to operate in line with WHO GMP requirements (noting that the four companies previously assessed by WHO as being GMP compliant were not included in the sample). The highest number of pharmaceutical manufacturers attained an overall GMP rating of "C" (13.5 manufacturers) closely followed by FPP manufacturers which obtained a "B" rating (11.5 manufacturers). The risk levels for compliance of QMS and site with WHO GMP requirements ranged from "1" to "3". This result verifies that the selection of manufacturers was suitable for the assessment, as the selection criteria were designed to define only FPP manufacturers that have not yet achieved full compliance with WHO GMP (no manufacturer with an overall GMP rating of "A" was included in the assessment), and to provide a representation of the different levels of GMP compliance to be found in the private sector (risk levels ranging from "1" to "3" could be observed).

Furthermore, this risk based categorization highlights the need for strategic guidance to improve existing GMP compliance, as the majority of manufacturers assessed received an overall "C" rating. This rating shows that the existing approach towards pharmaceutical manufacturing is not in line with WHO GMP and that a high risk exists with regard to production safety.

A comparison of risk levels assigned to site and QMS reveals that the highest number of FPP manufacturers (10.5 manufacturers) obtained an overall "C" rating due to a risk level of "3" for site related aspects. This means that these sites are impairing production safety and are therefore not suitable for pharmaceutical manufacturing. QMS was given a higher risk level than site related GMP aspects for only two manufacturers. These facts indicate that, in general, site related aspects of GMP are more significant than QMS when it comes to GMP non-compliance. Therefore, there is a strong need for guidance to manufacturers on design requirements for sites. Due to the high number of serious deficiencies related to site issues, and given that site related modifications are generally difficult, time consuming and quite costly, it is clear that the Roadmap towards WHO GMP requires a strong initial focus on improvement of site related GMP aspects.

Nevertheless, it should be pointed out in this context that the presence of only sporadically implemented quality management systems or the absence of an entire QMS is a significant deviation from WHO GMP and needs urgent improvement in order to ensure quality, safety and efficacy of the manufactured products. In addition, it has to be taken into consideration that the construction of new, WHO GMP compliant sites, or modification of existing manufacturing sites is time consuming and costly, whereas the required implementation of currently absent quality management systems

or the correction of existing quality management systems in line with WHO GMP requirements can be accomplished in a shorter timeframe and is generally less costly.

4.4.3. Conclusions drawn from the assessment

The following conclusions can be drawn from the assessment performed at pharmaceutical manufacturers in Nigeria:

- Site related GMP aspects need to be priority areas for improvement, but
- Only focusing on site during the first phase is not reasonable:
  - Immediate measures are also required to reduce risks caused by the QMS, and
  - Construction/modification of sites is time consuming due to the construction processes and the need to secure sufficient financial resources to fund the project, whereas implementation/correction of QMS can be performed in a shorter timeframe than site related work and is less costly.

These conclusions are reflected in the design of the Nigeria GMP Roadmap.

5 Components of the Nigeria GMP Roadmap

The design of the Nigeria GMP Roadmap document takes into account the outcomes of the baseline assessment of Nigerian manufacturers of finished pharmaceutical products conducted in 2017 and 2018 with regard to their existing level of compliance with WHO GMP (as described in section 4 of this document).

The Roadmap delineates a phased approach to WHO GMP compliance. Furthermore, it sets out requirements and milestones to be achieved during the progression of these manufacturers from their existing levels of GMP compliance up to full WHO GMP compliance over a specified period of time. In order to ensure that the Roadmap presents an achievable and hence realistic pathway towards full WHO GMP compliance, it is:

- Risk-based, taking into account the assessment results, and
- Structured in phases, allowing a stepwise improvement from the existing level of GMP compliance to full WHO GMP compliance with clearly defined targets at the end of each phase.

The Roadmap is intended to be a guidance tool covering aspects that need to be addressed in order to develop and implement site and quality management systems that are in line with WHO GMP requirements. It should be read in conjunction with respective WHO GMP guidelines.

The focus of the Roadmap lies on critical elements and systems which are common for manufacturers of medicinal products. The Roadmap is developed based on the 17 key elements of WHO GMP as outlined in section 4.2.2.

The baseline assessment revealed not only that improvement of site related GMP aspects need to be prioritized, but also that immediate measures are required in order to reduce risks caused by the quality management system (QMS). Therefore, the Roadmap focuses first on the establishment of a WHO GMP compliant site and on those quality management systems that have shown the severest deviations from WHO GMP.

Taking these results into account, the Nigeria GMP Roadmap delineates a **two-phased approach**.

5.1 Phase I

During the initial phase the focus of the Roadmap is placed on:

- Establishment of WHO GMP compliant manufacturing sites, and
- Those QMS related GMP aspects for which the majority of the FPP manufacturers showed least compliance.

Based on the key quality elements with the lowest compliance in Nigeria, the focus during phase I lies on the following key quality elements:

- Utilities impacting Good Manufacturing Practice (GMP)
- Qualification and validation
- Self-inspection, quality audits and suppliers' audits and approval
- Premises
- Materials
- Documentation
- Good practices in production
- Good practices in quality control
- Any site related aspects of other key quality elements

In addition to the above, the key quality element "Pharmaceutical Quality System" should be included in phase I, for a number of reasons:

- According to fig. 5, none of the manufacturers assessed showed acceptable compliance with this key quality element, and all manufacturers showed serious deficiencies resulting in either an "inadequate" or "improve" rating.
- The key quality element "Pharmaceutical Quality System" includes QMS related aspects such as change control, deviation handling, CAPA, quality risk management and product quality review which form the "backbone" of GMP for implementation of QMS aspects identified for phase I.
- A core focus during implementation of the GMP roadmap is on risk mitigation during the transition from current manufacturing practices to compliance with WHO GMP. This is especially the case where the implementation of corrections is not possible for serious deficiencies within a reasonable timeframe (for example where structural modifications to the site or the establishment of entire quality management systems are required), the manufacturer will have to define and implement adequate actions to mitigate identified risks until adequate corrections and corrective actions for the deficiencies are implemented. Quality risk management and CAPA are key aspects of the Pharmaceutical Quality System making this key quality element essential for adequate risk mitigation as well as CAPA preparation and implementation during the implementation of the Nigeria GMP Roadmap.

5.2 Phase II

The main focus during the subsequent phase is placed on establishing a comprehensive quality management system to ensure a systematic approach to WHO GMP.

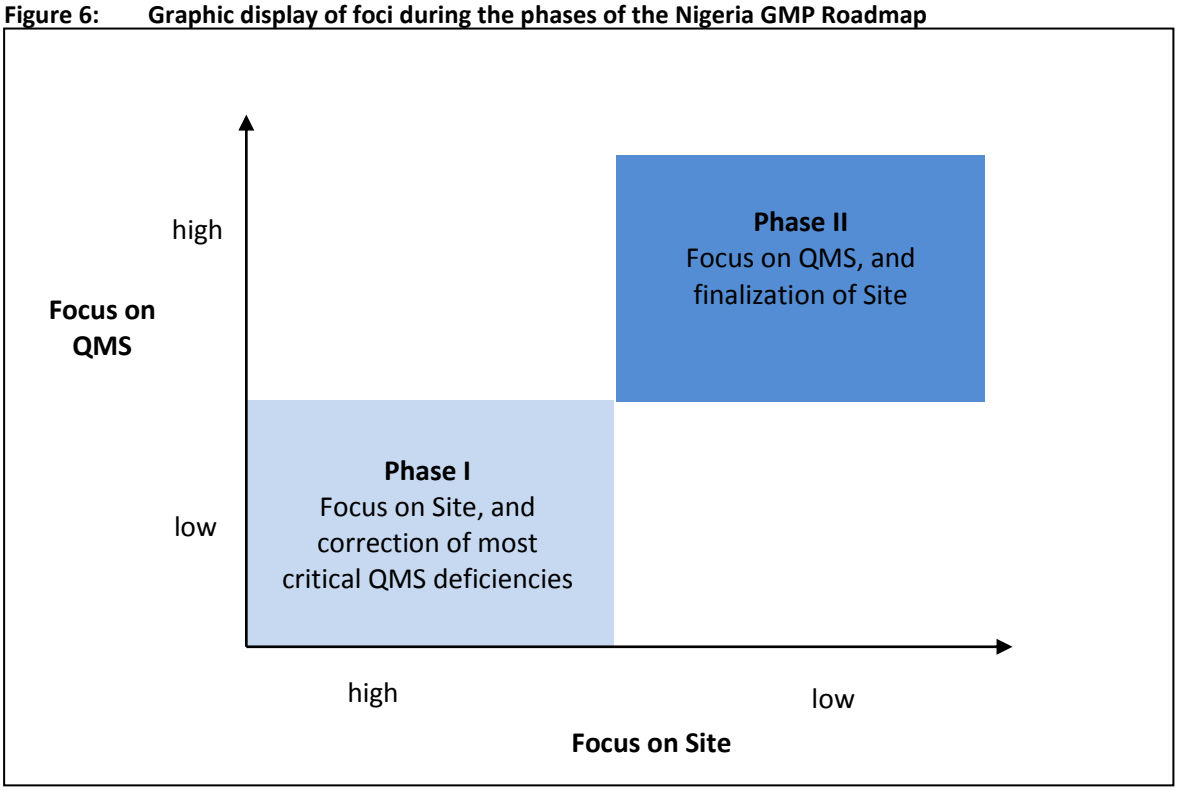
It is acknowledged that, depending on the extent of work required to establish WHO GMP compliant sites, finalization of construction related activities and/or site related documentation which has not been finalized during phase I might still be on-going during phase II.

The focus during phase II will be on the following key quality elements:

- Sanitation and hygiene
- Complaints
- Product recalls
- Contract production, analysis and other activities
- Personnel
- Training
- Personal hygiene
- Equipment

The different foci during the two phases of the Roadmap are presented graphically in figure 5, below.

Figure 6: Graphic display of foci during the phases of the Nigeria GMP Roadmap

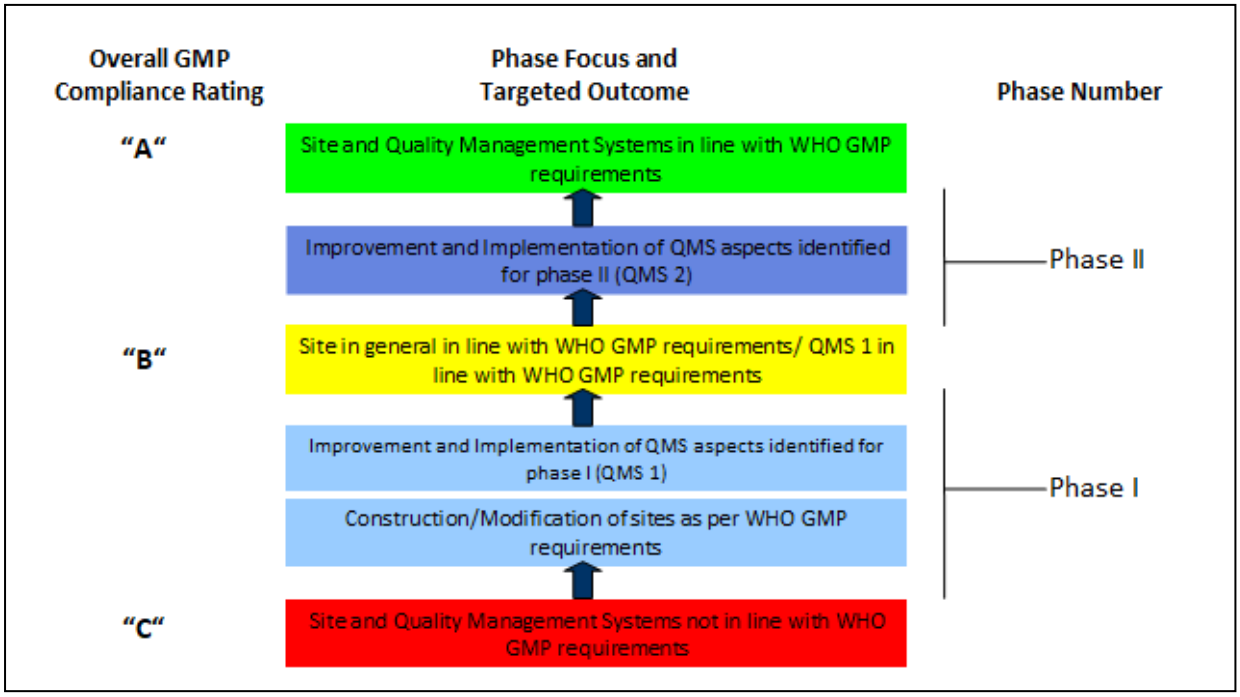


This phased approach will allow pharmaceutical manufacturers to make stepwise improvements from their existing compliance with GMP, towards full WHO GMP compliance. The risk assessment of the FPP manufacturers (refer to section 4.4.2) revealed that the majority of pharmaceutical manufacturers have been rated as class “C”, meaning “high risk manufacturers”, mainly due to the high risk associated with their sites. Phase I focuses on the establishment of WHO GMP compliant sites and on those quality management systems which showed severest deviations from WHO GMP. Using the results of the risk assessment, the majority of currently class “C” rated manufacturers following the phased Roadmap approach should reach a “B” rating at the end of phase I, as their sites, which are the main reason for their low GMP compliance rating, should then be in line with WHO GMP requirements. Those key quality elements for which the majority of manufacturers

showed least compliance will also be in line with WHO GMP requirements at the end of phase I, enabling manufacturers to have at least a sporadic implementation of QMS in place. During phase II, the main focus will be on establishing a comprehensive WHO GMP compliant QMS so that, after completion of phase II, both structural ("site") and organizational measures ("QMS") for GMP compliance will be in line with WHO.

This stepwise approach towards full WHO GMP compliance is graphically displayed in figure 6. The definition of the individual phases of the GMP Roadmap has been based on the severity of GMP deficiencies and on the compliance risk observed at Nigerian pharmaceutical manufacturers. Hence the stepwise, risk-based approach detailed in this document is based on the technical challenges faced by manufacturers in the country.

Figure 7: Stepwise approach towards achievement of full WHO GMP compliance, using the risk-based, phased approach of the Nigeria GMP Roadmap



Based on the results obtained from the WHO GMP compliance assessment of the Nigerian pharmaceutical manufacturers and on the phases derived above, a detailed technical Roadmap has been developed outlining required actions and milestones

- For improvement of Site related GMP aspects, and
- For improvement of QMS related GMP aspects throughout the phases of the Roadmap.

The Nigeria GMP Roadmap presents for each GMP relevant aspect:

- Scope/Definition of requirements,
- Design requirements/Content,
- Milestones for implementation.

The complete technical specifics of the Nigeria GMP Roadmap can be found in Annex A.

5.3 Utilization of the Roadmap

The Nigeria GMP Roadmap has been developed based on the results from on-site assessments of Nigerian pharmaceutical manufacturers and has been tailored to the specific situation in Nigeria. The technical reference standard for the Roadmap is WHO GMP as outlined in the document "Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2, 2nd updated edition. Good manufacturing practices and inspection. World Health Organization, Geneva, 2007" as subsequently updated through the WHO Technical Report Series (TRS), especially TRS 986, Annex 2. The Roadmap is intended to be a guiding tool encompassing the development of, and implementation requirements for, site and quality management systems in line with WHO GMP. As previously mentioned, it should be read in conjunction with respective WHO GMP guidelines. The Roadmap should be used as a stepwise tool to guide FPP manufacturers and regulatory authorities on the path towards WHO GMP:

- Already **existing manufacturers** can use the Roadmap together with the risk assessment in order to perform a gap analysis between their current and aspired compliance with WHO GMP requirements, and to follow a stepwise approach towards closing the gaps identified.
- **New start-up companies** can use this Roadmap to ensure that all necessary elements and systems are taken into consideration, and to check that they are in place before the actual launch of the company.
- The **regulatory authority** can use this Roadmap to review licensing criteria for new and existing facilities in order to improve them gradually until they are in line with WHO GMP requirements.

5.4 Targeted timeframe for implementation

For an individual FPP manufacturer, the timeframe for implementation of the Roadmap is highly dependent on the existing GMP compliance of the manufacturer, as well as on available financial, technical and human resource capacities. Nevertheless, the proposed timeframe targeted timeframe for the entire project could be in the range of 7 years, with

- The first phase targeted to take no longer than 5 years, and
- The second phase targeted to be completed within 2 years.

Distinct years for finalization of phase I and phase II will be determined after discussions with stakeholders including senior management of FPP manufacturers and finalization of the implementation plan for the GMP Roadmap. The time allocated to phase I is longer due to the need for modification of existing sites or construction of new sites during this phase.

Although the targeted timeframe of this Roadmap is proposed to be 7 years, it is acknowledged that the Roadmap has to be viewed as a working document during its implementation. It is also acknowledged that there is a need for continued development of the implementation plan, and for monitoring and review of the implementation process by a steering committee or a similar body.

Under the regional GMP Roadmap framework, it is proposed that maximum timelines for manufacturers in different ECOWAS Member States to reach the established milestones (B rating and A rating) are agreed, with individual countries able to opt to require accelerated compliance at their discretion. Decisions on the maximum timelines will be established through regional consultations.

6 Implementation of the Nigeria GMP Roadmap

Execution of the Nigeria GMP Roadmap requires an implementation plan that takes account multiple strategic components which are required for successful development of the industry and associated stakeholders. This includes the definition of near- and mid-term requirements that represent milestones or intermediate steps in the overall process.

One overriding requirement to successful implementation of the Roadmap is the continued support and buy-in to the process of key stakeholders from both private sector and Government. Specific aspects should be determined as part of a strategy for the development of the Nigerian pharmaceutical industry, which should take into account opportunities that would materialise as the ECOWAS regional market becomes increasingly defragmented. This strategy will be developed in conjunction with key stakeholders private sector and governmental bodies. It will need to consider inter alia administrative and governance-related matters, as well as technical, financial, incentive-related, human resources related, and advocacy related issues. These include:

- Establishment of a steering committee and working groups, or other form of governance structure, to provide the necessary direction, monitoring and review of the implementation process;
- Ongoing training, support and strengthening (as required) of NAFDAC to further build its capacity to assess and monitor manufacturers with regard to their level of GMP compliance and implementation of their CAPAs;
- Development of an approach for re-assessment and re-categorization of FPP manufacturers as they improve from their current manufacturing practices to compliance with WHO GMP. Under the regional GMP roadmap framework a process that includes an element of regional collaboration with regards to re-assessment is envisaged.
- Training of manufacturers with regard to WHO GMP requirements;
- Development of appropriate, time-limited incentive packages;
- Access to affordable finance for manufacturers, especially in the context of GMP compliant construction/modification of manufacturing sites;
- Training and provision of new personnel with sufficient GMP-related skills and general industrial pharmacy knowledge, to meet the HR needs of both pharmaceutical manufacturers and relevant supervisory/regulatory bodies;
- Promotion of partnerships and knowledge sharing between industrial pharmaceutical manufacturers.

The strategy will need to cover key dimensions for this range of activities, and others as identified by the relevant stakeholders, including the desired timeframes for individual components. It will also need to recognise the different types of support and opportunities that are required by

manufacturers at different stages of progression towards internationally recognised GMP compliance. For example early movers, that have made investments and are close to or at international GMP need market opportunities where the investment that they have made is rewarded with market opportunities whether, national, regional or from the international procurement funds.

III. SUMMARY OF THE REGIONAL GMP ROADMAP FRAMEWORK

7 Outline of the framework

The West African Health Organization (WAHO) has developed the ECOWAS Regional Pharmaceutical Plan (ERPP). This describes a comprehensive approach to improving access to essential medicines within the region. A central component of the plan is to reduce the reliance on imported products from outside the region. The document, as approved by Ministers of Health, includes the following mission: *"The ERPP seeks to lay down a strategic approach for member states to develop an efficient and effective pharmaceutical sector that would manufacture and supply safe and good quality medicines, for national regional and international markets".*

WAHO has been working with UNIDO since 2017 to develop a regional GMP roadmap framework for the ECOWAS pharmaceutical manufacturing industry to attain internationally recognised GMP standards. The work has been termed, in short, the "ECOWAS Regional GMP Roadmap Framework project". This approach provides an overarching framework that has been developed using data from all countries and under which national level technical approaches for companies to advance towards and meet internationally recognized GMP standards have been developed. Nigeria has by far the largest pharmaceutical manufacturing sector in the region and the results from the assessments that have informed the specifics of this national roadmap document have been central to designing the regional framework. Hence the national roadmap is in line with the overarching parameters established by the framework. Through alignment of all national level roadmaps with a unanimously validated approach, ultimately international standards can be reached across the board and risks during the transition can be mitigated such that increasingly (subject to rigorous product development and approval processes) products are quality assured as being safe and efficacious.

A framework for the region is necessary given that defragmentation of the regional market will be beneficial for all, and one critical consideration to achieving this is that a common set of standards is applied. However, the situation in 2019 as regards manufacturers in the ECOWAS region is highly heterogeneous both between countries and within countries. When considering individual member states, Nigeria has well over 100 manufacturers, Ghana has at least 25 active manufacturers whilst others have 4 or less and some do not currently have pharmaceutical manufacturers. Within countries, standards of production vary significantly as has been demonstrated by the baseline assessment process that is described in this document.

It is also important to note that upgrading manufacturing standards is a long-term endeavour and requires not only technical insights and expertise but the combination of many other factors that create an enabling environment for manufacturers to source investment, technology and human resources amongst other requirements. Manufacturers need support and guidance to develop their businesses and time to implement the upgrading plans that result. In the short to medium term, the risk of dangerous products entering the market from licensed manufacturers can be mitigated through various approaches as described in this document. However, ultimately adherence to GMP is the best way to assure the quality of the products that are produced at each manufacturing site.

8 Baseline assessments of company GMP compliance

The baseline assessments were conducted across the region in all countries where manufacturing occurs using the same methodology as for the assessments that informed the development of the Nigeria Roadmap.

9 Insights from assessments for design of framework

The findings from the assessments have informed the structure of the framework in that it:

- Provides a consistent methodology for categorization of the level of GMP compliance
- Provides comprehensive technical guidance and targets across all sub components of the 17 key quality elements (particularly given that deficiencies vary between countries and companies and hence tailoring the framework to the specific situation inter alia requires such a document).
- Utilizes a risk based, 2 step phased approach for upgrading of existing manufacturers with established timelines for companies to achieve an overall compliance rating of B (i.e. medium risk) and then A rating (i.e. low risk – largely compliant with WHO GMP).
- Includes agreement that all new manufacturers should be GMP compliant prior to receiving a manufacturing license.
- Includes measures to mitigate risk during the transition to WHO GMP compliance.

Additionally, the framework recognises that not all manufacturers start at the same point and that guidance for the more advanced companies on achieving international standards in the short term would be beneficial as it could enable/expedite their ability to access international donor funded markets.

10 Key features of the framework

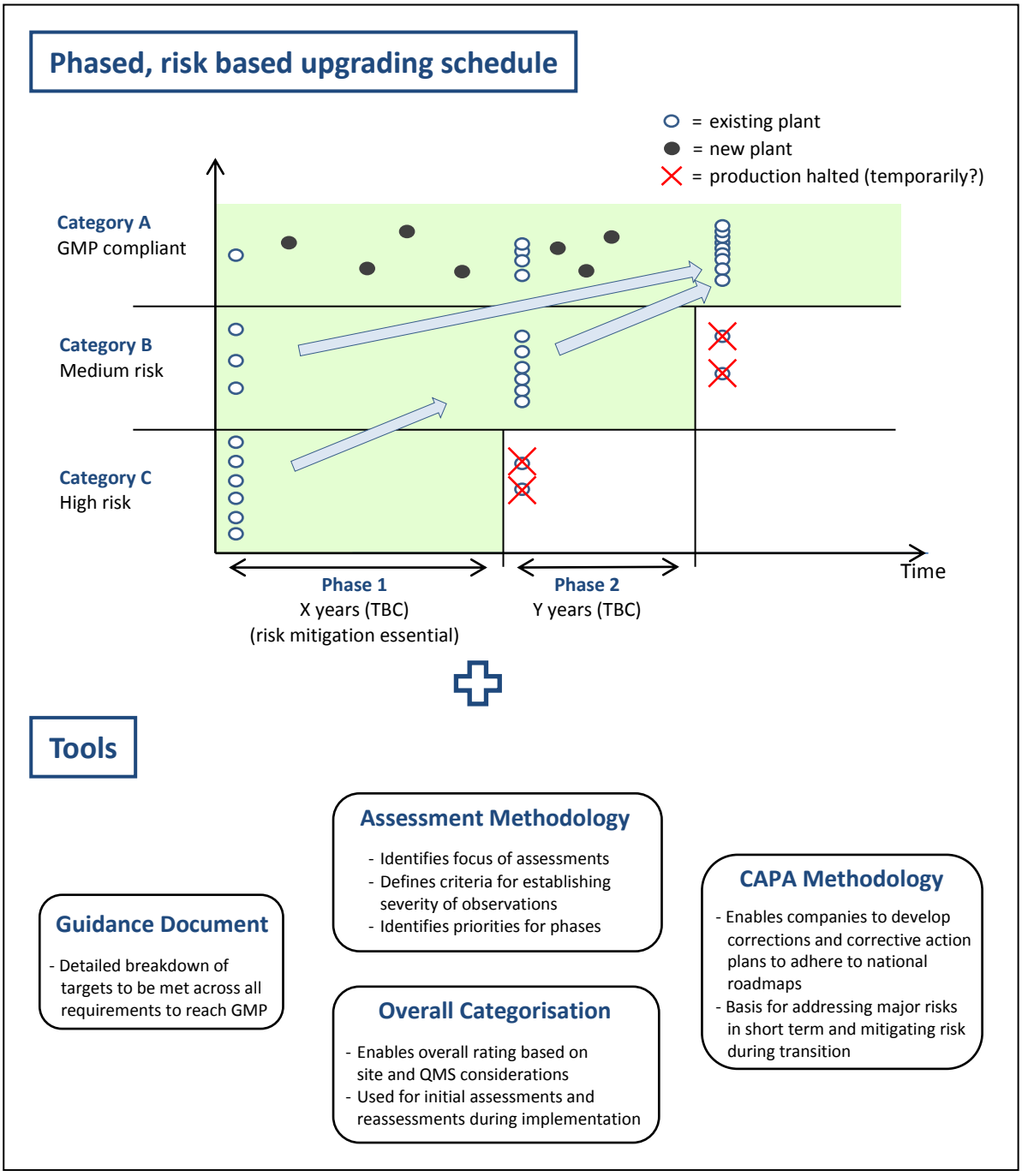
The framework consists of tools (as utilised in the development of the Nigerian Roadmap) and guidance as well as a risk based phased schedule for upgrading standards. It includes a guidance document that breaks down each of the 17 key quality elements into technical specifics and defines actions and milestones for implementation separating out those that pertain to site related and QMS related aspects of GMP

The upgrading schedule includes the following which enable tailoring to the specific country context as has been done for this Nigerian GMP roadmap. These are:

1. A stepwise phased approach to upgrading GMP standards with phase 1 involving all manufacturers reaching at least a B rating and step 2 involving all manufacturers reaching a rating of A, in line with WHO GMP. (The timelines for each phase need to be determined through regional negotiations early on in an implementation phase)
2. Risk based approach where the technical deficiencies that pose the most significant threat to safety are addressed first.
3. Measures to mitigate production related risk during the transition towards WHO GMP standards.

4. The requirement that all new facilities meet WHO GMP standards before they are licensed for manufacturing.

Figure 8: Schematic representation of the key components of the Regional GMP Roadmap Framework



11 Key benefits of the approach

Through utilizing this framework and the associated national GMP roadmaps in conjunction with a comprehensive implementation plan:

- Industries across the region can follow a unified approach to upgrading and ultimately reaching WHO GMP;

- All new manufacturing companies will meet internationally recognized standards from the start of operations thereby avoiding the costly and time consuming process for upgrading.
- More advanced companies can reach internationally recognised standards in the relatively near term, a key requirement for accessing the international donor markets;
- Risk to public health can be mitigated whilst companies upgrade to internationally recognised standards.

12 Validation of Framework

The Regional GMP Roadmap Framework for ECOWAS member states was validated in December 2018 at the Third Regional Workshop, held in Abidjan, Ivory Coast and attended by WAHO, UNIDO, Members of the ERPP GMP working group, regulators from all ECOWAS member states, Industry from all manufacturing countries, and local partners. The meeting was chaired by the President of the West African Pharmaceutical Manufacturers Association**.**

13 Relationship between the ECOWAS Regional Roadmap Framework and the Nigeria national roadmap

The Nigeria GMP Roadmap is a technical document that sets out a step wise phase approach for upgrading current manufacturing in the country to internationally recognized standards. It also outlines key considerations that need to be taken into account to ensure that any new pharmaceutical manufacturing operations that are established in the country are compliant with internationally recognized GMP standards before they are licensed for commercial production. It is relevant to key national level stakeholders

This document is consistent with the regional framework and provides more country specific qualitative and technical insights that should inform the development of the national approach to meet the targets established at the regional level.

It is recognized that, whilst representative members of each ECOWAS member state have been involved in the process of developing the regional framework, decision-making in relation to implementation of the upgrading process at the national level involve the respective stakeholders in the country concerned. Therefore, whilst the framework and each national level roadmap are designed to be complementary, implementation in Nigeria of the country specific roadmap in relation to existing manufacturers, new companies and related matters requires that it be led by key national stakeholders, with support from WAHO, UNIDO and other partners, as required.

IV. CONCLUSION

This national GMP roadmap describes a risk based phased, approach for developing the pharmaceutical manufacturing industry in Nigeria so that technical shortcomings in manufacturers' compliance with internationally recognized GMP standards can be addressed. The GMP standard referenced in this document is WHO GMP, which is universally acknowledged and with which compliance is a pre-requisite for WHO prequalification of products to supply international procurement entities. The roadmap covers sterile and non-sterile formulations of small molecule medicines but is not applicable to the production of complex biological products.

It has been developed through a collaboration between NAFDAC, PMGMAN and UNIDO with support from WAHO as part of an ECOWAS regional project to establish common principles for developing the pharmaceutical industry in West Africa.

Historically, a number of Nigerian organizations including NAFDAC and PMGMAN as well as PSN have been active in striving to strengthen the sector through technical and policy initiatives as well as advocacy and capacity building. Objectives of these undertakings include a reduction of Nigeria's reliance on imports for its pharmaceutical needs, a reduction in the level of sub-standard products entering the market and in so doing, an increase in access to safe, effective, affordable medicines.

This roadmap for the pharmaceutical industry to move towards internationally recognized levels of GMP compliance has been developed utilising UNIDO's GMP Roadmap methodology. A representative sample of manufacturers was identified and then assessed by recognized international experts to establish a baseline understanding of the existing levels of compliance to WHO GMP that manufacturers adhere to. Based on detailed observations made during manufacturing facility visits across representative geopolitical zones the key technical challenges that Nigerian manufacturers face in firstly conducting safe manufacturing and secondly adhering with the full requirements of international GMP were established. This methodology also allowed for a categorization of GMP compliance along two axes, namely quality management systems and physical aspects of the facilities (site). Combining the findings for these two dimensions provided an overall risk level for each manufacturer assessed based on a scale of A (low compliance risk), B (medium compliance risk) and C (high compliance risk).

It should be noted that the four companies that had been assessed by WHO as being GMP compliant were deliberately excluded from the sampling. Whilst these leading companies were not assessed, no other companies were identified as being A rated. Overall compliance risk levels could be attributed to 25 of the manufacturers that were assessed. 11.5 were found to be medium risk and 13.5 high risk (note: one company had a B level sterile facility and a C rated non-sterile facility). In all cases the assessed risk level for site was worse than or equal to the rating for QMS.

Based on these results a two phased approach has been developed. The detailed foci of each stage are described in Annex A below. The main objective of phase 1 is to ensure that all companies are operating at a minimum of a B rating (medium risk) by the end of this phase. Given that all companies with a C rating had significant critical observations related to site, a main focus of phase 1 is to address the physical dimensions of manufacturing operations that pose a high risk to production safety. The first phase of the roadmap also includes implementing the main components of a functioning QMS.

The second phase of the roadmap would be expected to be shorter than phase 1 given that the key foci are on finalizing any remaining site related issues and on upgrading to a comprehensive QMS. Given that a significant proportion of manufacturers were found to be B rated already, there should be a number of companies that can reach a low risk level equivalent to WHO GMP compliance well within the duration of the GMP Roadmap.

Timelines of three years for phase 1 and two years for phase 2 are recommended. However establishing specific dates by which companies need to reach these milestones requires further national level consultations given that a conducive environment is necessary to enable companies to adhere to the roadmap, and this requires initiatives on multiple fronts to be put in place. This is also consistent with the regional GMP roadmap framework, under which further consultations are required to establish maximum timelines for the different phases that all countries in the region agree to.

This Nigeria GMP Roadmap approach was presented to stakeholders including senior representatives from NAFDAC, PMGMAN, the Federal Ministry of Health, USP and others at a validation workshop in April 2019, where it received endorsement from those present.

The contents of this document are aligned with the Regional GMP roadmap framework that was presented to representatives from all ECOWAS member states in November 2018 at a regional workshop in Abidjan. This framework was validated by the meeting which was attended by representatives from all regulatory entities from the 15 ECOWAS Member States, pharmaceutical manufacturers from across the region and their presentative bodies including PMGMAN and the West African Pharmaceutical Manufacturers Association, and other stakeholders including the African Development Bank and USP. The comparability of findings detailed in this roadmap with those across the region based on a standard, calibrated methodology will enable other entities in the region to make informed decisions about sourcing from Nigerian manufacturers based on a common understanding of their level of compliance with GMP, a factor that will become increasingly relevant as the sector develops across the region and companies progress towards lower risk manufacturing.

This document, the result of an extended collaboration between NAFDAC, PMGMAN and UNIDO, describes a pragmatic approach to strengthening the industry, recognizing that time and support are required to enable manufacturers to invest in meeting internationally recognized GMP standards and that at least one interim step is required for many companies. It provides the tools and prioritisation of issues that will enable risk to production safety to be mitigated during the upgrading process. It is aligned with the ECOWAS Regional framework which will form the central component of a long term comprehensive programme which that addresses the multiple aspects required to establish a conducive context for pharmaceutical manufacturing in the ECOWAS region. It will support the development of the industry and, as required, associated stakeholders in Nigeria as well as smaller sectors in other countries in the region. In so doing, pharmaceutical manufacturing in Nigeria can develop to be commercially viable at internationally recognized standards and to increase the range of products that are currently manufactured in the country. The industry can thus be supported to increase its contribution to the economic development of the country and to improve access to safe, effective, affordable medicines for Nigerians in particular as well as citizens of other ECOWAS Member States.

ANNEX A: NIGERIA ROADMAP TOWARDS WHO GMP – TECHNICAL SPECIFICS

The technical specifics of the Nigeria Roadmap towards WHO GMP were developed following a baseline assessment of Nigerian pharmaceutical manufacturers of medicinal products regarding their existing level of compliance with WHO GMP.

Based on results obtained from these assessments a phased, risk-based approach to compliance with WHO GMP[2] has been developed. The baseline assessment has revealed that site related GMP aspects need to be priority aspects for improvement, but also that immediate measures are required in order to reduce risks caused by the quality management system (QMS).

Therefore, the Roadmap focuses first on the establishment of a WHO GMP compliant site and on those quality management systems for which the severest deviations from WHO GMP have been identified.

The Roadmap delineates a two-phased approach, as shown diagrammatically in figure 6. In summary:

- **Phase I** focuses on the establishment of WHO GMP compliant manufacturing sites (section 1.1) and on those QMS related GMP aspects for which the majority of the companies showed least compliance as well as the establishment of a Pharmaceutical Quality System (section 1.2);
- **Phase II** focuses on the establishment of a comprehensive quality management system ensuring a systematic approach to WHO GMP (section 2).

The Roadmap delineates the key elements to be implemented in a structured approach to improve existing GMP standards to the required WHO GMP standards. It sets out requirements and milestones for pharmaceutical manufacturers to be achieved as they progress from the existing level of GMP compliance to full WHO GMP compliance over a specified period of time.

[2] The technical reference standard for the Roadmap is WHO GMP as outlined in the document "Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2, 2nd updated edition. Good manufacturing practices and inspection. World Health Organization, Geneva, 2007" as subsequently updated through the WHO Technical Report Series (TRS), especially TRS 986, Annex 2. The Roadmap intends to be a guiding tool to set and successively meet crucial requirements for site and quality management systems in line with WHO GMP. The Roadmap document shall be read in conjunction with the respective WHO GMP guidelines.

START: Site and Quality Management Systems not in compliance with WHO GMP requirements

SECTION 1.1: PHASE I, SITE

Phase/ Reference number	Key quality element	Actions for implementation	Milestones
1.1.1	Premises[i]*	Define scope of premises by taking into account: • Environment in which the premises are built • Targeted product classes (e.g. if toxic, sensitizing, mutagenic, beta-lactams, sensitive to light, temperature and/or humidity, sterile/non-sterile, dosage forms) • Targeted production capacity (e.g. annual number of tablets, volumes, packs, etc.) and manufacturing environment for targeted product classes • Manufacturing operations to be performed at site • Storage capacities and required environment for materials and products • Product development activities to be performed at site ("pure" manufacturing site vs. R&D/scale-up plus manufacturing) • Process ancillary, technical and social areas • Availability, generation and distribution of utilities • Administrative areas (e.g. for record keeping, archiving, training) • Total area of land The design of a typical stand alone facility typically includes following areas: • Warehousing including receipt and dispatch areas • Cleanrooms for sampling, dispensing and processing • Clean support areas (such as washing, movements and staging) • Packaging areas • Quality control laboratory • Process ancillary areas and equipment • Utilities	Scope of the premises defined. Design specifications and layout for premises in place and approved by authorities. Personnel and material flow defined. Supply of utilities defined and adequate space allocated.

		The design of the premises should
		• Ensure logical flow of materials and personnel
		• Minimize the risk of errors and mix-ups
		• Permit effective cleaning
		• Prevent accumulation of dirt and dust
		• Provide suitable technical controls to prevent contamination and cross-contamination
		• Provide containment measures adequate for the operations and materials/products handled
		• Define suitable construction materials
		• Provide suitable environment for all operations taking place at site
		• Provide segregation of manufacturing operations performed at site
		• Permit effective maintenance
		• Permit adequate space for operations taking place
		• Prevent access of unauthorized personnel from entering site
		• Within the site prevent access of unauthorized personnel to production, storage areas and the quality control laboratory
		• Provide airlocks for personnel and material
		• Ensure separation of controlled from uncontrolled areas by realization of adequate zone concepts, including:
		  ○ Separation of quality control laboratories from production areas
		  ○ Separation of rest and refreshment room from manufacturing quality control and warehousing areas
		  ○ Separation of maintenance workshops from production areas
		  ○ Separation of areas for secondary and subsequent packaging operations from cleanroom areas
		• Allow for effective pest control
		• Protect materials and products during receiving and dispatch procedures from weather and pest intrusion
		• Ensure separation of receiving and dispatch areas
		• Provide storage areas of sufficient capacity, adequate environment and security for the various categories of materials and products with proper separation and segregation
		• Provide utilities required and suitable space for generation and distribution
		• Provide back-up power to run essential operations in the event of power failures
		• Provide a suitable drainage system which has	

		hygienic design and is able to prevent back-flow • Provide dedicated, self-contained areas in case sensitizing/hazardous products are manufactured • Provide segregated areas in case medicinal and non-medicinal products are manufactured • Provide separation of warehouses for raw material, packaging materials and finished goods from production areas • Provide emergency installations (eye wash, emergency showers, firefighting equipment, etc.) Establishment of suitable contractors* and support staff for construction of site Construction of premises complying to the design specifications	Suitable contractors and support staff identified and contracted Premises complying with predefined specifications in place. Facility, as constructed, is conforming to original design drawings.
1.1.2	Utilities impacting Good Manufacturing Practice	<u>Water:</u> Identification of the required water qualities needed for the operations to be performed at the site Identification of a water source suitable for the generation of the identified water qualities Definition of (pre-) treatments required of the source water to obtain water in the required qualities. Taking into account the quality of the source water, the water qualities to be used within the site and the	Required water qualities needed for intended operations identified Suitable water source (e.g. borehole or public water) identified. Quality of source water identified. Requirements for water treatment defined. Design specifications

		water consumption of the site, specifications and design of a water treatment plant are established for (where necessary) pre-treatment of source water to achieve potable water and for generation of required compendial water qualities. The design assures that major contaminant groups such as particulates, inorganics, organics and microbes are removed by the system. The water distribution system has to ensure that the water generated is not adversely affected during its circulation through the system and its intended period of use, e.g. by selection of a suitable of material of construction such as SS 316L, selection of suitable pumps, valves and welding techniques such as orbital welding, the design of a loop system and the avoidance of dead legs. The system has to be suitable for cleaning and sanitization procedures and has to be drainable. The system allows sampling after at least each major purification step and for monitoring of the quality of the generated water circulating within the system.	and layout of water treatment plant available. Position of sampling points defined and identified.
		Establishment of suitable supplier(s)* for components of water treatment plant	Suitable supplier(s) identified and contracts available
		Installation/Commissioning of the water treatment plant and distribution system complying to the design specifications	Water treatment plant and distribution system complying with predefined specifications and design in place. As-built system conforms to original design drawings.
		<u>Environmental control (Heating, Ventilation, Air conditioning):</u> Assessment of environment in which the pharmaceutical manufacturing plant is going to be set up, product range, activities performed within the site and volumes of the cleanroom areas.	Assessment performed.
		Taking into account the environment in which the site is going to be constructed, the product range, activities to be performed within the site and the	Requirements for environmental

		volumes of the cleanroom areas the requirements for environmental control (such as acceptable number of particulates, air changes, pressure cascades, temperature, humidity) are defined. The design and extent of the environmental controls are based on a zone concept and assure that a cleanroom environment suitable for pharmaceutical manufacturing is created. The system is designed to prevent the areas within the factory from cross-contamination and contamination as well it prevents contamination of the environment outside the factory. The design of the system is suitable for the zone concept selected for the facility and allows for monitoring/control of functionality of the zone concept and environmental attributes.	controls defined. Design specifications and layout of Heating, Ventilation, Air Conditioning units available. The system allows monitoring/control of critical attributes such as environmental attributes and functionality of the zone concept.
		Construction of adequate areas for filter cleaning ensuring containment commensurate with the risk identified for materials handled	Filter cleaning areas ensuring containment commensurate with the risk identified for materials handled in place
		Establishment of suitable supplier(s)* for Heating, Ventilation, Air conditioning systems	Suitable supplier(s) identified and contracts available
		Installation/Commissioning of the Heating, Ventilation, Air conditioning and distribution systems complying to the design specifications	Heating, Ventilation, Air conditioning and distribution systems complying with predefined specifications and design in place. As-built systems conform to original design

			drawings.
		<u>Compressed Dried Air (CDA):</u> Based on the intended use(s) of CDA, required quality(s) are defined.	Requirements for CDA defined including intended use(s) and quality(s).
		Taking into account the intended use(s), environment(s) in which CDA is utilized, required pressures and volumes at site and product groups manufactured, the CDA system is designed to remove contaminants such as oil, water, particles and bio burden to the extend required and allows for monitoring of critical attributes including pressure and dew point.	Design specifications and layout of CDA system available. The system has provisions for monitoring of critical attributes.
		Establishment of suitable supplier(s)* for CDA system(s).	Suitable supplier(s) identified and contracts available
		Installation/Commissioning of the CDA generation and distribution system(s) complying to the design specifications	CDA generation and distribution system(s) complying with predefined specifications and design in place. As-built system conforms to original design drawings.
		<u>Steam</u> Evaluation of the need for steam generation and distribution system(s)	Evaluation regarding the need for steam system(s) finalized.
		Based on the intended use(s) of steam, required quality(s) are defined	Intended use(s) of steam and steam qualities defined.
		Taking into account feed water quality, intended	Design

		use(s) of steam, required steam quality(s) and volumes, specifications and design of steam generation and distribution system(s) is/are established allowing monitoring and treatment of the steam to the extend required. Establishment of suitable supplier(s)* for steam system(s). Installation/Commissioning of the steam generation and distribution system(s) complying to the design specifications	specifications and layout of steam system available. The system has provisions for monitoring of critical attributes. Suitable supplier(s) identified and contracts available. Steam generation and distribution system(s) complying with predefined specifications and design in place. As-built system conforms to original design drawings.
1.1.3	Materials	Taking into consideration the targeted production capacity and the types of materials used for production the design of separate storage areas for • starting materials • packaging materials • intermediates • bulk products • finished products and for separate product statuses such as • quarantined • released • rejected • returned • recalled is done ensuring orderly storage of the different categories of materials and products. Taking into consideration the product range, appropriate storage conditions are defined with focus	Design specifications and layout for areas for storage, sampling, dispensing and material transport are in place. Areas complying

		on environment, required monitoring devices, cleanability, space and security to avoid any alteration of material and product during storage. The design has to ensure segregation of receiving and dispatch areas, that during receipt and dispatch materials and goods are protected from weather and that an effective pest control can be implemented. Access to storage, esp. to storage of labels, printed packaging materials and controlled substances, production and quality control areas has to be restricted to authorized personnel only. Based on the product classes manufactured the manufacturing activities and the production capacity of the site a suitable flow of material and product through the various manufacturing steps is defined. Areas for sampling and dispensing of materials have to provide adequate space, environment and equipment to prevent mix-ups and (cross-) contaminations during the operations performed. Furthermore, dust control measures need to be in place ensuring adequate containment.	with original specifications and design
1.1.4	Good practices in production	(covered in section 1.1.1: Premises)	(covered in section 1.1.1: Premises)
1.1.5	Good Practices in Quality Control	Definition of analytical activities which have to take place in the quality control laboratory based on the product range and manufacturing activities performed at the site. Design of layout of the laboratory and definition of equipment required to perform all analytical controls effectively and reliably are carried out taking into consideration: • Location and containment requirements in order to ensure adequate separation of the quality control laboratory from production areas • Restriction of access to laboratory and its storage areas • Adequate space, environment and equipment to prevent mix-ups and (cross-)contaminations during inspecting, testing of materials, products and environmental monitoring • Ensure logical flow of samples, reagents and personnel • Sufficient number of rooms and areas to ensure that the testing systems are separated and do not interfere with each other. • Utilities required for operations to be performed including back-up systems or stabilizers for equipment which need uninterrupted power supply	Analytical activities defined Design specifications and layout for premises and equipment are suitable for performance of quality control activities.

		• Separation of air handling between laboratory and production • Separation of storage of samples, retained samples and reagents, laboratory accessories and reference materials • Separation of storage areas from testing areas • Suitability of storage areas with focus on size, safety and environment for storage of reagents, reference materials, solvents, samples, archiving of documentation and for performing stability studies • Suitability of laboratory equipment, instruments and environments for the analytical tests to be performed • Appropriate range and precision of measuring equipment • Suitability of equipment for required calibration, qualification procedures • Type and quality of calibration standards needed • Safety of operations • Availability of emergency equipment • Appropriate waste handling Establishment of suitable contractors* and supplier(s)* for construction, equipment procurement, and servicing of laboratory. Design and equipment of laboratory complying to the design specifications and layouts	Suitable contractors and suppliers identified and contracts available Design and specifications of laboratory and equipment complying with original design and specifications
1.1.6	Equipment	Identification of equipment needed based on product classes to be manufactured, production capacity, operational and control requirements and quality control activities to be performed at the site. Definition of specifications, design and location of equipment to assure suitability of the equipment for its intended purpose taking into consideration requirements such as: • Operational environment • Containment requirements • Material requirements, esp. for product	Equipment needed identified Design specifications and layout/drawings of equipment and support systems

		contact areas, including ○ Type of construction materials ensuring that the materials are not reactive, additive or absorptive or adsorptive ○ Requirements on surface finishes/roughness • Cleanability / sterilization requirements • Prevention of (cross-) contamination • Maintenance which should have as little impact on clean room production processes as possible (e.g. by “through the wall” installations) • Ease of change-over • Use of suitable lubricants and coolants • Suitability of equipment for calibration procedures • Type and quality of calibration standards needed • Appropriate range and tolerances of measuring equipment • Appropriate equipment number and capacity of equipment taking into consideration change-over and process cycle times • Suitability of dimensions and weight of equipment for its intended location of use • Controls and automatization concept • Required space and access to equipment for operation • Utilities/support systems needed for operation • Safety of operation • Need for adequate labelling at point of operation	available.
		Establishment of suitable supplier(s)* for equipment.	Suitable supplier(s) identified and contracts available
		Installation/Commissioning of equipment complying to the design specifications	Equipment complying with predefined specifications and design in place. As-built equipment conforms to original design drawings.

1.1.7	Personnel/ Personal hygiene	Based on product range, operational steps, production capacity and controls required define the number and qualification of personnel required. Taking into consideration the product classes, the operations to be performed at the site and the number and qualifications of personnel required at site the design of site and equipment have to assure that • rest and refreshment rooms are separated from production and control areas with no direct access to them • only authorized personnel can enter restricted areas the design of entrances to uncontrolled and • controlled areas is spacious and suitable to prevent contamination/cross-contamination of adjacent areas and to perform the required entrance procedures • direct contact of personnel and materials/ products is avoided • flow of personnel is not negatively impacting on the quality of products manufactured The working and protective garments of staff have to be suitable for the operations to be performed and the areas of work. Separate protective clothing shall be in place for areas in which sensitizing/hazardous products are manufactured. Availability of adequate premises, equipment and technical measures to ensure containment of sensitizing/hazardous products and to prevent cross-contamination of materials and products due to personnel flow and cleaning of garments.	Number and qualification of personnel defined Design specifications and layout for premises and equipment are suitable with regards to personnel and hygiene. Implementation is done complying with original specifications and designs Suitable garments for staff defined and implemented Adequate premises, equipment and technical measures in place ensuring containment of sensitizing/hazardous products and preventing cross-contamination of materials and products due to personnel flow and cleaning of garments.

Site compliant with WHO GMP but
Quality Management Systems not in line with WHO GMP

SECTION 1.2: PHASE I, QUALITY MANAGEMENT SYSTEMS

Phase/ Reference number	Key quality element	Actions for implementation	Milestones
1.2.1	Pharmaceutical Quality System	Development of an organizational structure (organogram) within the company outlining hierarchy, functional levels and reporting lines. The organizational structure has to ensure a separation of quality assurance/control from production. Preparation of "Master" documents outlining the quality management system, such as quality manual, site master file, validation master plan, outlining organizational structure, responsibilities, procedures, processes and resources required for implementation Preparation of written key procedures for the key elements of the quality management system including procedures for • Certification/Release of products to the market and rejection thereof • Change control • Deviation management • Corrective and preventive actions • Regular evaluations of quality (e.g. Quality audits, Product quality review, periodic document review, management review) • Ensuring quality, safety and efficacy of the products manufactured throughout their life-cycle Development and implementation of a system for quality risk management defining applicability, responsibilities and procedures	Authorized organizational charts in place Documented quality management system in place and implemented Written procedures for quality assurance in place and implemented Quality risk management system in place and implemented

1.2.2	Premises	Development and implementation of a documentation system containing procedures, protocols, reports and records for qualification, maintenance, cleaning and sanitization of premises	Documentation system for qualification, maintenance, cleaning and sanitization of premises in place and implemented
		Development and implementation of a program for pest control outlining procedures and specifications for pest control, locations, frequency, the need and qualifications for contractors* including agreements.	Documented program for pest control including procedures for contractors in place and implemented
		Development of a system defining the room status (e.g. clean, in operation, awaiting cleaning, under maintenance) within operational sections	Documented system for defining room status in place and implemented
1.2.3	Utilities impacting Good Manufacturing Practice	Development and implementation of a system containing documented procedures, protocols, reports and records for calibration, qualification, maintenance, cleaning and sanitization for each equipment	System containing documented procedures, protocols, reports and records for calibration, qualification, maintenance, cleaning and sanitization for each equipment in place and implemented
		Development and implementation of documented procedures for operation of utilities including records/logbooks for each equipment	Documented procedures for operation of equipment including records/logbooks for each equipment in place and implemented

		Development and implementation of systems visualizing content and flow directions of pipe works	Systems visualizing content and flow directions of pipe works in place and implemented
		Development of a system defining the equipment status	System for defining the equipment status in place and implemented
		Establishment of specifications, action and alert limits, sampling procedures, sampling frequencies and test methods	Documented specifications, sampling procedures, frequencies and test methods in place and implemented
		Establishment of a continuous monitoring and reporting program for utilities directly impacting product quality	A program for continuous monitoring and reporting in place and followed
1.2.4	Qualification and validation	Development and implementation of master documentation for calibration, qualification and validation activities (Validation master plan and Project plans) outlining approach (risk based), procedures, responsibilities, schedules, management of all lifecycle stages and documentation requirements	Master documentation in place and implemented
		Development and implementation of plans, protocols and reports for calibration, qualification and validation procedures including documented procedures, plans and reports for (re-)calibration, (re-)qualification and (re-)validation of buildings, utilities, equipment, controls, processes and methods as outlined in the validation master plan	Plans, protocols and reports for (re)-calibration, (re-) qualification and (re-) validation in place as outlined in the Validation Master plan and implemented

		Development and implementation of systems for review and tracking of calibration, qualification and validation activities and status	Systems for review and tracking of calibration, qualification and validation activities and status in place and implemented
1.2.5	Self-inspection, quality audits and suppliers' audits and approval	Development and implementation of a system for self-inspections including • Inspection program • Inspection frequency • Composition of inspection team, training requirements and responsibilities • Record and classification of audit observations • Reporting of observations • Corrections and corrective actions • Evaluation of effectiveness of actions taken Development and implementation of a system for manufacturer and supplier audits and approval including • Procedure and criteria for evaluation of compliance of manufacturers and suppliers of starting and packaging materials regarding suitability, legality and GMP compliance • Identification of audit needs and audit requirements for manufacturers and supplier; prioritization of audit requirements and preparation of audit schedules • Pre-audit, audit and post-audit follow up procedures for manufacturers and suppliers • Establishment of criteria and procedures for qualification of manufacturers and suppliers for which no audit need has been identified • Definition of qualification and disqualification criteria for manufacturers and suppliers and related procedures • Requirement to establish quality/technical agreements with manufacturers and suppliers • A list of approved manufacturers and suppliers for starting and packaging materials • Procedure, criteria and periods for monitoring and re-evaluation/re-qualification of manufacturers and suppliers of starting and packaging materials	Self-inspection procedures developed and implemented Procedures for manufacturer and supplier qualification in place and implemented

1.2.6	Materials	Development and implementation of documented systems and procedures for receipt, handling, sampling, inspecting, release, rejection, dispensing, distribution and destruction of materials, labels, intermediates and finished products and defining authorized personnel performing these operations including: • Development and implementation of procedures ensuring that only materials of quality adequate for their intended use are purchased, received and handled • Definition of transportation and storage requirements for materials and products handled • Definition and implementation of procedures to ensure transportation and storage of materials and products in a suitable environments with restriction of access where necessary • Definition and implementation of procedures for sampling, identity and integrity check of incoming consignments • Definition and implementation of procedures for labelling, storage and handling of materials, labels, intermediates and products according to their status effectively preventing any mix-ups of materials with different status and clearly defining authorized personnel for access and status change • Development and implementation of a system for unique identification of materials and products including identification code/batch numbers, sampling status, storage location and number of containers • Definition and implementation of procedures for stock rotation (e.g. first-expiry-first-out) and expiry control • Definition and implementation of procedures for regular stock reconciliation comparing actual versus recorded stocks • Definition and implementation of procedures for issuing and reconciliation of materials and products • Definition and implementation of procedures for dispensing of materials and handling of dispensed materials • Definition and implementation of procedures to ensure adequacy and traceability of the distribution process • Definition and implementation of a pest control program ensuring that measures taken for pest control do not lead to contamination	Documented systems for receipt, handling, sampling, release, rejection, dispensing, distribution and destruction of materials and products in place and implemented

		of equipment, materials and products. • Definition and implementation of procedures for reworking/reprocessing or recovery of rejected products • Definition and implementation of procedures for proper and safe storage and disposal of waste	
1.2.7	Documenta-tion	Development and implementation of a documentation system containing: • Master documents defining control of the documentation system as well as format, content, date and time conventions, preparation, multiplication without alteration, issuance and distribution to the place(s) of use, traceability, version control practices, review and authorization, periodic reviews, storage, archiving and destruction of documents such as: ○ SOPs ○ Specifications and testing procedures ○ Logbooks ○ Records ○ Labels ○ Master formulae (providing detailed information on material quality and quantity, batch size, all manufacturing steps, process parameters, in-process and environmental controls, line-clearance instructions, yield and reconciliation procedures) ○ Manufacturing/packing instructions and records (batch-specific, allowing full traceability of batch history) • A system for records and record keeping ensuring traceability and integrity of data and records/logbooks • Referencing of records/logbooks/labels to their governing SOPs • Definitions for GMP-conform corrections and alterations • A system for document and data control in electronic media (including access control, authorizations for data entries and changes) • A master index of all procedures, forms and current version numbers allowing traceability of revision history	Comprehensive documentation system in place and implemented

		• Documents derived from master documents defining specifications, procedures, logs and records for all type of materials, products, operations, methods of manufacturing, quality and environmental controls, maintenance, cleaning, sanitization and labelling including their issuing departments and dates, validities, functional areas, objectives and scopes, change histories, references, authorities and responsibilities of personnel involved • Distribution registers for controlled documents • Definition of label formats and labelling practices	
1.2.8	Good practices in production	Development of a system to identify and classify substances handled regarding their potency, hazardous or sensitizing potential and to derive containment requirements based on the classification done. Development and implementation of organizational procedures to avoid contamination and cross-contamination and ensuring containment to the extent required taking into account the risks associated to the materials and products handled; these procedures should further disallow in general the manufacture of different products within the same room.	System to identify and classify substances handled regarding their potency, hazardous or sensitizing potential and to derive containment requirements based on the classification in place and implemented Organizational procedures to avoid contamination and cross-contamination and ensuring containment to the extent required in place and implemented
		Development and implementation of procedures and records for all production related activities including in-process and environmental controls, line-clearance and reconciliation procedures	Procedures and records for all production related activities including in-process and environmental

			controls, line-clearance and reconciliation procedures in place and implemented
		Development and implementation of written procedures for all manufacturing and packaging activities carried out, also reflecting results of qualifications/validations performed	Written procedures for all manufacturing activities carried out, also reflecting results of qualifications/ validations performed in place and implemented
		Development and implementation of labelling practices of materials, containers, equipment, rooms, lines, pipelines identifying operational status, product/material processed, strength, batch number, production stage and details of previous product/material as required.	Labelling practices in place and implemented
		Development and implementation of organizational measures avoiding mix-ups between non-sterilized and sterilized materials and products	Organizational measures avoiding mix-ups between non-sterilized and sterilized materials and products in place and implemented
		Development and implementation of procedures for handling of unused un-coded and coded packaging materials	Procedures for handling of unused un-coded and coded packaging materials in place and implemented

1.2.9	Good Practices in Quality Control	Development and implementation of procedures, records and registers covering all operations performed in the laboratory including:	Procedures, records and registers covering all operations performed in the laboratory in place and implemented including:
		Definition and implementation of documented procedures including records and logs for the entire sample flow from sampling, sample labelling, sample receipt, storage and chain of custody until completion of testing up to issuance of test report or certificate of analysis allowing full traceability of sample history, standards/reagents and quality thereof, equipment, methods, personnel involved	Documented procedures including records and logs for the entire sample flow allowing full traceability in place and implemented
		Definition and implementation of environment and control procedures suitable for the various tests performed	Environment and control procedures suitable for the various tests performed defined and implemented
		Development and implementation of systems and schedules for validation, verification procedures for analytical methods and processes and calibration, qualification procedures for utilities, equipment, and computerized systems	Systems and schedules for validation, verification, calibration, qualification procedures in place and followed
		Development and implementation of servicing and maintenance procedures for equipment	Servicing and maintenance procedures for equipment in place and followed
		Development and implementation of a training and periodic evaluation scheme for analysts.	Training and periodic evaluation

			scheme for analysts in place and implemented
		Development and implementation of procedures, logs and records for operation and suitability testing of equipment, methods used	Procedures, logs and records for operation and suitability testing of equipment, methods used in place and implemented
		Development and implementation of issuing procedures and records for samples, standards, reagents and controlled documents	Issuing procedures and records for samples, standards, reagents and controlled documents in place and implemented
		Development and implementation of procedures and records for stock control	Procedures and records for stock control in place and implemented
		Development and implementation of procedures for handling of test results including raw data and worksheets/laboratory notebooks, records ensuring traceability and authenticity/integrity of data	Procedures for handling of test results including raw data and worksheets/laboratory notebooks, records ensuring traceability and authenticity/integrity of data in place and implemented
		Development and implementation of procedures for release of test results/analytical reports and certification	Procedures for release of test results/ analytical reports and

			certification in place and implemented
		Development and implementation of a system ensuring that all required reference standards, reagents, solvents and culture media in the required quality are available	System ensuring that all required reference standards, reagents/solvents and culture media in the required quality are available in place and implemented
		Development and implementation of procedures, records and logs for handling of reagents, solvents, culture media including required quality, identification of suppliers, receipt, identification/labelling, storage, expiration dating, issuance, use, master formulae for preparations of reagents and culture media, procedures for standardization and suitability testing where appropriate	Procedures, records and logs for handling of reagents/solvents, culture media including required quality, identification of suppliers, receipt, identification/labelling, storage, expiration dating, issuance, use, master formulae for preparations of reagents and culture media, procedures for standardization and suitability testing where appropriate in place and implemented
		Development and implementation of documented procedures, records and logs for handling of chemical reference standards including quality, source, procurement, receipt, labelling, storage, issuance, use, duration of use and lot number control	Documented procedures, records and logs for handling of chemical reference standards in place and

			implemented
		Development and implementation of documented procedures for preparation and handling of chemical in-house reference and working standards including details on reference material, preparation/ standardization, retesting and re-standardization, labelling, storage, issuance, use, duration of use	Documented procedures, records and logs for handling of chemical in-house reference and working standards in place and implemented
		Development and implementation of procedures for handling of out of specification results (OOS) and out of trend results (OOT) addressing a phased approach consisting of initial laboratory investigations followed by full scale investigations as well as hypothesis testing, number and justification for of retesting and resampling	Procedures for out of specification results (OOS) and out of trend results (OOT) in place and implemented
		Development and implementation of documents defining specifications and testing procedures for all raw materials, packaging materials, intermediates, bulk and finished products	Documents defining specifications and testing procedures for all raw materials, packaging materials, intermediates, bulk and finished products in place and implemented
		Development and implementation of programs for stability testing in line with WHO/ICH requirements	Stability programs in place and implemented in line with WHO/ICH requirements
		Development and implementation of a system for drawing, handling, storage and inspection of retention samples	System for drawing, handling, storage and inspection of retention

			samples in place and implemented
		Definition and implementation of appropriate garment and safety procedures for protection of operator and environment and to avoid any contamination of samples	Appropriate garment and safety procedures in place and implemented
		Development and implementation of procedures for waste handling	Procedures for waste handling in place and implemented
END OF SECTION: PHASE I, QMS			

Site and QMS identified having most critical impact on product safety, quality and efficacy in Nigeria compliant with WHO GMP

SECTION 2: PHASE II

Phase/ Reference number	Key quality element	Actions for implementation	Milestones
2.1	Sanitation and hygiene	Development and validation of suitable cleaning procedures for premises, equipment and garments to the extent required taking into consideration that the cleaning procedure must not have a negative impact on materials and products handled. Cleaning tools used must be suitable and must not become a source of (cross-) contamination. Storage of cleaned equipment and garments must not become a source of (cross-) contamination.	Suitable cleaning procedures developed and successfully validated.
		Development of a cleaning program outlining requirements and training needs of personnel, premises, equipment, material, garments to be cleaned, cleaning procedures, cleaning frequencies, cleaning and disinfection agents. This program has to be accompanied by a schedule and a log to trace the activities done.	A comprehensive cleaning program including schedule and logs is in place and followed.
		Development of a routine environmental monitoring program including specifications, action and alert limits, sampling procedures and frequencies for evaluation.	Routine environmental monitoring programs are developed and implemented.
2.2	Complaints	Development and implementation of a documented	Documented

		system regarding handling, investigation, corrections and corrective actions of complaints containing: • Responsible person(s) and responsibilities • Procedures to be followed for handling, risk classification, investigation, corrections and corrective actions of complaints including timelines • The need to extend investigation to other batches, materials, products • Investigation of possible counterfeiting • The need for product recall • The need to inform competent authorities and public in case of a public risk • Registration system for complaints received, investigations and actions performed • Regular review and trending of records	system for handling, investigation, corrective and preventive actions of complaints in place and implemented
2.3	Product recalls	Development and implementation of a documented recall procedure containing: • Responsibilities of personnel involved in recall procedure/composition of Recall committee • Classification of recall and actions to be taken based on the severity of reason for the recall including timelines • The need to inform competent authorities and public in a timely manner in case of public risk • Procedures to be followed for handling, investigation, corrections and corrective actions • The need to extend investigation to other batches, materials, products • Reconciliation of recall • Registration and trending system for recall and activities performed as part of the recalls • Storage and labelling of recalled products • Procedures to verify functionality and adequacy of recall system as well as to enable for continuous improvement	Documented system for recall procedure in place and implemented
2.4	Contract production, analysis and other activities	Based on product range, analytical requirements and activities performed in-house evaluation of the need for contract production, analysis and other outsourced activities is done. Development and implementation of documented procedures to ensure that contract production, analysis and other outsourced activities are performed in accordance to the marketing authorization of the product and in line with GMP requirements containing: • Pre-requisites to be fulfilled before contract	Needs for contract production/analysis identified Documented procedures for contract production/analysis in place and implemented

		production/analysis and other outsourced activities take place including evaluation of potential contract acceptor regarding legality, suitability and competence • Written agreements between contract giver and acceptor detailing responsibilities, knowledge management, attributes impacting quality or traceability of product/service, release and documentation procedures, access of the contract giver to records and raw data, re-evaluation of contract acceptor and, where needed, sub-contractors • List of approved contract organizations	
2.5	Personnel	Establishment of adequate number of personnel required and development of written procedures for establishment of job descriptions Definition of necessary qualifications, experiences and responsibilities in form of job descriptions ensuring that key personnel responsible for supervising the production and quality unit(s) for pharmaceutical products possesses the qualifications of a scientific education and practical experience required by national legislation. Development and implementation of mechanisms and procedures for restriction of access to site, production, storage and quality control laboratory	Number, qualifications and experience of personnel defined Signed and dated job descriptions for personnel in place Mechanisms and procedures in place and implemented for restriction of access
2.6	Training	Development and implementation of documented training procedures including: • Training needs assessment • Training program for induction, on-job and continuing training • Training schedules • Training requirements for trainers • Training frequency • Control of training attendance • Assessment of effectiveness of training and handling of personnel failing assessment • Training records including their review and update procedures • Training requirements for external support staff/contractors	Training procedures in place and implemented
2.7	Personal hygiene	Development and implementation of documented procedures to ensure GMP-conform personal hygiene	Documented procedures

		including: • Entrance and exit procedures for the various sections of the site which are suitable to prevent (cross-)contamination especially in cases where sensitizing/hazardous products are manufactured • Suitable protective clothing concept for the various sections of work • Separate protective clothing for areas in which sensitizing/hazardous products are manufactured • Suitable laundering procedures to prevent contamination of garment during laundry and drying • Signs visualizing hygienic requirements such as washing, sanitization and gowning procedures • Health examination program for personnel at beginning of employment and at defined frequencies • Sensitivity testing of staff handling sensitizing materials and products • A procedure restraining ill, injured personnel or personnel with open lesions from working close to open product • Prohibition of eating, drinking and smoking material and personal medicines in production, quality control areas and warehouse areas • Training programs on personal hygiene	ensuring GMP-conform personal hygiene in place and implemented
2.8	Equipment	Development and implementation of a system containing documented procedures, protocols, reports and records for calibration, qualification, maintenance and cleaning, sanitization for each equipment Development and implementation of documented procedures for operation of equipment including records/logbooks	System containing documented procedures, protocols, reports and records for calibration, qualification, maintenance and cleaning, sanitization for each equipment in place and implemented Documented procedures for operation of equipment including records/logbooks

			in place and implemented
		Development of a system defining the equipment status (e.g. clean, in operation, awaiting cleaning, under maintenance) within operational sections	Documented system for defining equipment status in place and implemented
		Development and implementation of documented procedures for handling of defect equipment and support systems	Documented procedures for handling of defect equipment and support systems in place and implemented
END OF SECTION: Phase II			

COMPLETION: Site and Quality Management Systems in compliance with WHO GMP

* Establishment of suitability of contractors, suppliers and support staff includes the evaluation of their legality and competence.

** Sewage, refuse, and other waste (e.g., solids, liquids, or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely, and sanitary manner. Containers and/or pipes for waste material should be clearly identified (adopted from ICH Q7). Additionally, the handling of all waste shall be in line with national requirements.

APPENDIX I: KEY QUALITY ELEMENTS AND FOCUS OF ASSESSMENTS

This Appendix details the key quality elements, subsections and focus areas during the assessment of manufacturers.

WHO GMP requirements have been defined in 17 key quality elements. Each key quality element has been divided into sub-sections for which the assessment focus has been defined. Key quality elements together with defined subsections and the focus areas during assessment of the key quality elements are outlined in Table 1.

Table 1: Key quality elements, defined subsections and focus during assessment

Key quality elements	Subsections	Focus during assessment
1. Pharmaceutical Quality System	General	Master documents including Site Master File, Validation Master Plan, SOP for SOPs, quality manual
	Management responsibilities	• Organogram • Job descriptions • Separation between Quality Assurance/Control and production → Functionality of Quality Assurance/ Control department
	Release of finished products for market	• Release/ rejection procedure and records • Checklist for batch review • Certification / authority for batch release
	Deviations	• Applicability of procedure • Responsibilities • Procedure for reporting, investigation, corrective and preventive actions, recording • Records • Trending
	Corrective and preventive action	• Applicability of procedure • Responsibilities • System for identification, investigation, corrective and preventive action, follow-up, evaluation of effectiveness, review • Records, trending
	Change Control	• Applicability of procedure • Responsibilities • System for request, evaluation/classification, implementation, post-implementation assessment, close-out • Records, trending

Key quality elements	Subsections	Focus during assessment

1. Pharmaceutical Quality System (ctd.)	Regular evaluations of product quality and quality management system	• Product Quality Review, incl.
		  ○ System
		  ○ Content
		  ○ Applicability of procedure
		  ○ Responsibilities
		  ○ Review period, timelines
		  ○ Trending/ statistical evaluation
		  ○ Use of results for continuous improvement
		  ○ Conclusions drawn
		• Management reviews
		• Self-inspection procedures (details point 8)

	Quality Risk Management	• Applicability • Responsibilities • Procedure • Documentation • Review

2. Utilities impacting GMP requirements	HVAC	• Need for separate systems
		• Level of filtration (Filter specifications)
		• Recirculation or fresh air
		• Location of filters
		• Position of inlet and air return, dust extractors
		• Room classifications
		  ○ Temperature
		  ○ Humidity
		  ○ Air changes
		  ○ Particulates
		  ○ Microbes
		• Pressure differentials
		• Design of ducting
		• Easy and effective cleaning
		• Alarm system
		• Air flow direction
		• Compliance of design specifications and drawings with reality
		• Qualification and re-qualification procedures
		• Labelling of ducting
		• Monitoring of HVAC system (e.g. particles, microbes, humidity, temperature, pressure differentials)
		Operation, maintenance, calibration, SOPs, records for HVAC including breakdown/ emergency programs

Key quality elements	Subsections	Focus during assessment
2. Utilities impacting GMP requirements (ctd.)	Water system	• Feed water quality • Water quality(ies) being used within the plant and purpose of use • Suitability of construction materials and purification steps used • Welding • Slope of pipeworks, drainability • Labelling of pipework • Recirculation at adequate velocity and temperature • Capacity and daily demand • Valves • Positioning of sampling and user ports • Easy and effective cleaning and sanitization • Alarm system • Compliance of design specifications and drawings with reality • Labelling of sampling and user ports • Qualification and re-qualification procedures • Monitoring of system and water quality/ Quality control testing • Operation, maintenance, calibration, SOPs, records
	Steam	• Types of use of steam • Suitability of steam generated for its use • Feed water quality • Suitability of generation and distribution system • Compliance of design specifications and drawings with reality • Labelling of sampling and user ports • Qualification and re-qualification procedures • Labelling of ducting • Monitoring of system and steam quality/ Quality control testing • Operation, maintenance, calibration, SOPs, records

Key quality elements	Subsections	Focus during assessment
2. Utilities impacting GMP requirements (ctd.)	Compressed dried air	• Generation of compressed dried air • Level of filtration (Filter specifications) • Location of filters • Water separation • Dew point • Design of ducting/distribution system • Easy and effective cleaning • Alarm system • Air flow direction • Capacity and daily demand • Compliance of design specifications and drawings with reality • Labelling of ducting • Qualification and re-qualification procedures • Monitoring of system (e.g. oil, particles, microbes, dew point, filter integrity) • Operation, maintenance, calibration, SOPs, records
3. Sanitation and hygiene	Sanitation and hygiene program	• Program in place including personnel, premises, equipment, materials, containers, cleaning/ disinfection agents, frequencies • Suitability of cleaning and sanitation agents used • Procedures, records, logs • Routine environmental monitoring program • Sanitization, disinfection of drains • Disinfectant efficacy testing • Garment cleaning/laundry

Key quality elements	Subsections	Focus during assessment
4. Qualification and validation	Validation Master Plan	Approach, content, procedures, responsibilities, schedules and documentation requirements for (re-) calibration, (re-) qualification and (re-) validation activities, regular review of calibration/ qualification/validation status and activities
	Qualification/calibration of equipment and utilities	• Schedules • Calibration frequencies • Elements of qualification (DQ, IQ, OQ, PQ) • Protocols • Reports • Ratio of equipment/utilities qualified/calibrated to unqualified/not calibrated • Handling of non-qualified, non-calibrated equipment/utilities • Responsibilities • Standards used and traceability of standards • Tracking/labelling of calibration/qualification status
	Process validation	• Type(s) of process validation in place • Schedules • Protocols/reports • Responsibilities • Definition of acceptance criteria • Ratio processes validated to not validated • Handling of non-validated processes
	Analytical method validation	• Schedules • Protocols • Reports • Responsibilities • Definition of acceptance criteria

Key quality elements	Subsections	Focus during assessment
4. Qualification and validation (ctd.)	Analytical method validation (ctd.)	• Ratio methods validated to not validated • Handling of non-validated methods
	Cleaning validation	• Schedules • Approach: product specific vs. equipment specific • Determination of worst case(s) • Holding times clean/dirty • Protocols/reports • Responsibilities • Definition of acceptance criteria • Ratio cleaning procedures validated to not validated • Handling of non-validated procedures
	Automated and computerized systems	• Schedules • Handling of stand-alone systems • Handling of in-build systems • Responsibilities • Protocols • Reports
	Re-qualification and revalidation	• Criteria for re-qualification and revalidation • Use of annual reviews to determine need for re-qualification and revalidation
5. Complaints	Handling of complaints	• Responsibilities • Procedure for handling, investigation, corrective/preventive actions • Risk classification • Evaluation of need for recall • Registration/records • Regular review/trending
6. Product Recalls	Handling of product recalls	• Responsibilities • Procedure for handling, investigation, corrective/preventive actions • Risk classification • Mock recall • Registration/records • Regular review/trending • Number and reasons for recalls

Key quality elements	Subsections	Focus during assessment
7. Contract production, analysis and other activities	Control of external contract work	• Responsibilities • Assessment/evaluation of contractors • Re-assessment/evaluation of contractors and frequency • Auditors and qualification • Recording, classification, reporting of observations • Contracts/agreements • Records
8. Self-inspection, quality audits and suppliers' audits and approval	Self-inspections and quality audits for evaluation of regulatory and GMP compliance	• Approach • Departments inspected • Frequency • Responsibilities • Auditors and qualification • Recording, classification, reporting of observations • CAPA program • Evaluation of effectiveness of CAPA
	Vendor audits and approval	• Responsibilities • Assessment / evaluation • Number of vendors audited • Rational for exclusion of vendors from audits • Re-assessment/evaluation procedure and frequency • Auditors and qualification • Recording, classification, reporting of observations • Follow-ups • Contracts/agreements • List of approved vendors
9. Personnel	General	• Adequacy of number of personnel
	Job descriptions	• SOP • Example job descriptions for key personnel • Authorities and key responsibilities • Delegation of functions • Signed by employer and staff
	Key personnel	• Qualifications, experience • Full-time employment • Ratio of QA personnel to number of operational personnel
	Access authorizations for production, storage and QC areas	• Access control to facility • Access control restricted areas within the facility

Key quality elements	Subsections	Focus during assessment
10. Training	Training of personnel	• Training needs assessment • Training program and schedule • Types of trainings • Content of trainings • Training requirements for trainers • Training frequency • Control of training attendance • Assessment of effectiveness of training • Training records including their review and update procedures • Training requirements for external support staff/contractors
11. Personal hygiene; occupational health and safety	Occupational health and safety	• Suitability of garments/personal protective equipment • Emergency installations (eye wash, emergency showers, firefighting equipment, etc.) • Health examination programs and frequencies
	Hygiene measures	• Personal hygiene procedures • Protective clothing • Prohibition of eating, drinking and smoking material and personal medicines • Restrain of ill, contagious staff from working in open product areas
	Training	• External vs. internal training • See point 10
12. Premises	General	• Location • Design/layout and comparison with reality • Materials of construction and finishes • Suitability for operations, cleaning and sanitization • Written preventive maintenance and cleaning/sanitation procedures and records • Logical flow of materials, products and personnel • Suitability of design for pest control • Installations for pest control
	Cleanliness zoning	• Clean zone and containment concept • Separation of areas • Room status labelling

Key quality elements	Subsections	Focus during assessment
12. Premises (ctd.)	Ancillary areas	• Separation of rest and refreshment rooms form manufacturing and QC • Appropriate changing rooms • Toilets with no direct access to production/storage areas • Maintenance workshops separate from production
	Storage areas	• Capacity for proper storage and separation and control of various categories of materials/products and material/product status • Adequate storage conditions • Separation of receiving and dispatch areas • Receiving and dispatch areas → protection from weather and pest intrusion • Storage of flammables and controlled substances • Sampling areas for starting and packaging materials
	Weighing areas	• Separation for starting materials and intermediates/products • Dust control • Cleanability and cleanliness • Environment
	Production areas	• Layout • Sequence of operations, clean zones • Space • Cleanability • Suitability of drainages • Prevention of contamination and mix-ups
	QC areas	• Separation of quality control laboratory from production areas • Restriction of access • Design, layout • Space, environment • Flow of samples, reagents and personnel • Separation of testing procedures and areas • Separation of air handling between laboratory and production • Storage areas • Safety of operations • Availability of emergency equipment • Waste handling

Key quality elements	Subsections	Focus during assessment
13. Equipment	General production and QC equipment, support systems	• Availability of equipment and support systems • Drawings of critical equipment and support systems • Support systems for power back-up and uninterrupted power supply (UPS) • Suitability for use, maintenance and cleaning • Maintenance procedures, schedules, logs • Status labelling • Handling of defect equipment/support systems • Operating procedures/logs • Labelling of fixed pipework
14. Materials	Storage and distribution	• Status labelling and authority for status change • Material handling system (FIFO/FEFO), stock cards vs. computer based • Traceability of material handling • Storage areas for starting, packaging materials, labels, intermediates and products • Stock control procedures • Material identification/labelling • Handling and storage of materials/products with different release status • Release status control • Expiry control
	Lubricants/coolants	• Food grade status of lubricants/coolants in case of product contact
	Starting materials	• Material quality • Purchase, receiving, storage, handling and control • Procedure defining storage conditions of starting materials • Material codes/manufacturer specific batch numbers • Procedure/checklist for receipt of materials and investigation of damages observed during receipt • Identity of each container • Dispensing procedures and handling of dispensed materials • Sampling procedures

Key quality elements	Subsections	Focus during assessment
14. Materials (ctd.)	Packaging materials (primary or printed packaging material)	• Material quality • Purchase, receipt, storage, handling and control • Material codes/manufacturer specific batch numbers • Procedure/checklist for receipt of materials and investigation of damages observed during receipt • Sampling and dispensing procedures • Access control for printed PM • Use of feed rolls, indication of splicing • Handling of unused materials
	Intermediate and bulk products	• Batch numbering system • Storage, handling and control • Sampling procedures
	Finished products	• Batch numbering system • Storage, handling and control • Sampling procedures • Product distribution records • Traceability of distributed products
	Rejected, recovered, reprocessed and reworked materials	• Handling, storage, control and labelling of non-conforming materials and products • Procedures for reworking/ reprocessing or recovery of rejected products
	Recalled products	Storage/control/labelling
	Returned goods	Storage/handling/control/labelling/ decision on further use
	Reagents and culture media	• Storage, receipt and labelling
	Reference standards	• Storage, receipt and labelling of primary standards • Storage and labelling of working standards
	Waste material/materials awaiting destruction	• Storage before disposal • Procedure, methods and frequency of disposal • Destruction of printed packaging materials and labels before disposal • Adherence to local laws/ regulations
	Agents for pest control	• Suitability of rodenticides, insecticides and fumigating agents

Key quality elements	Subsections	Focus during assessment
15. Documentation	Defined instructions and procedures; system for elaboration, multiplication, checking, approval, regular review and version control	• System/Procedures/Master documents • Responsibilities • Alteration and correction of documents • Distribution to places of use • Document/data control in electronic media
	Record keeping	• Systems for records in manufacturing, QC and distribution • Traceability and integrity if data • Traceability of sample history, standards/reagents and quality thereof, equipment, methods, personnel • Traceability of documents/batches • Referencing of records to their governing SOPs
	Labels	• Practice for material, equipment, room identification and status control • Version control practices • Label control/issuance • Label content, initialization, dating
	Logbooks	• Content • Availability for equipment, utilities, components, procedures, rooms • Referencing of logbooks to SOPs • Version control practices
	Specifications and testing procedures for starting and packaging materials, intermediates, bulk and finished products	• Design, content, review, authorization, distribution and version control practices • Availability of approved specifications for all GMP-relevant material • Referencing to quality standards • Availability of pharmacopoeias
	Test records	• Design, content, review, authorization, issuance, distribution and version control practices • Handling of electronic data/data generated by computerized systems • Traceability • Methods for preparation of working documents from master documents

Key quality elements	Subsections	Focus during assessment
15. Documentation (ctd.)	Master formulae/Batch processing records	• Design, content, review, authorization, issuance, distribution and version control practices • Availability of documents, protocols and records for manufacturing including line clearance, sampling, testing, monitoring, review and release requirements with signatures and authorizations • Batch traceability • Methods for preparation of working documents from master • Recording of deviations • Documentation of reconciliation practices
	Packaging instructions / records	• Design, content, review, authorization, distribution and version control practices • Availability of documents, protocols and records for packaging, coding and labelling including line clearance, sampling, testing, monitoring, review and release requirements with signatures and authorizations • Traceability • Methods for preparation of working documents from master • Recording of deviations • Documentation of reconciliation of labels and printed packaging material
	SOPs and associated records	• System, incl. authorization, issuance, distribution and version control, prevention of use of unauthorized copies • Referencing of records/logs to related SOP • List of SOPs/master indices
	Archiving	• Requirements for various types of documents and records • Traceability/retrieval procedure for archived documents • Type/format for archiving • Storage conditions • Security/back-up policy

Key quality elements	Subsections	Focus during assessment
16. Good practices in production	Prevention of cross-contamination and bacterial contamination during production	• Prevention of dissemination of dust; supply air control • Measures to avoid contamination of starting materials and products by other material and products • Cleaning • Environmental monitoring during processing operations
	Processing operations	• Access control to production premises • Segregation of operations • Exclusion of production of non-medical products • In process controls • Line clearance practices, incl. documentation • Reconciliation and investigation of reconciliation discrepancies
	Packaging operations	• Segregation of products • Measures to minimize risk of cross-contamination and mix-ups • Line clearance practices, incl. documentation • Check of printing operations • In process controls • Reconciliation and investigation of reconciliation discrepancies • SOP for return of unused materials to stock
17. Good practices in quality control	General	• Independence of QC from production and other departments • Facilities, equipment and personnel • Initiation of sampling and testing • Equipment used for testing • Rooms, environment for testing • Authenticity of data/data integrity • Retention samples: Handling, storage, registration, labelling, frequency of drawing of retention samples • OOS/OOT procedures • Servicing, maintenance procedures, agreements • Safety/waste handling

Key quality elements	Subsections	Focus during assessment
17. Good practices in quality control (ctd.)	QC of starting and packaging materials, labels, intermediates, bulk and finished products	• Handling of incoming samples and prevention of (cross-) contamination • Adherence to test procedures, defined quality, specifications and records • Availability, use, handling, maintenance, issuance and where appropriate testing and release of reference standards • Procedures for preparation, standardization, labelling, use, handling, maintenance, issuance, testing and release of in-house reference and working standards • Microbial testing, reference strains • Sample handling including receipt, registration, storage, issuance for testing • Handling, storage of reagents, standards and culture media • Procedures, records for preparation, handling and issuance of reagents and culture media • Controls to verify suitability of culture media • Logs, registers • Issuance of controlled documents • Labelling • Cleaning procedures
	Test requirements	• Requirements for testing starting, packaging materials, labels, intermediates, products • Release procedures, authorities • Approval/Certification procedures • Evaluation of analyst performance • System suitability testing
	Batch record review	• Inclusion of QC records during batch record review and investigation of discrepancies/failures
	Stability studies	• Stability testing programs • Protocols • Reports • Schedules • Registers • Stability conditions and monitoring of conditions • Establishment of shelf-life

APPENDIX II: ASSESSMENT SCHEDULE APPLIED DURING FIELD STUDIES

Based on defined key quality elements of WHO GMP and assessment focus areas an assessment schedule has been prepared which will be uniformly applied for the assessment of Nigerian pharmaceutical manufacturers regarding their existing level of compliance to WHO GMP. Each manufacturer was assessed for two full working days. The assessment schedule is displayed in table

Table 1: Assessment schedule for the baseline assessment of Nigerian pharmaceutical manufacturers regarding their existing level of compliance to WHO GMP

<table>
<tr><th colspan="2">Day 1</th></tr>
<tr><td rowspan="6">Morning</td><td>Arrival</td></tr>
<tr><td>Introductions</td></tr>
<tr><td>Objectives and scope of assessment</td></tr>
<tr><td>Site master file</td></tr>
<tr><td>Organizational structure</td></tr>
<tr><td>Site layout</td></tr>
<tr><td>Afternoon</td><td>Factory tour:
Warehouses
Receiving area and stores
Starting and packaging materials
Sampling and issuing
Production
Utilities with direct impact on product quality, such as
HVAC system
Water system
Compressed air system</td></tr>
</table>

Table 1 (continued): Assessment schedule for the baseline assessment of Nigerian pharmaceutical manufacturers regarding their existing level of compliance to WHO GMP

Day 2	
Morning	Factory tour (ctd.): Quality control laboratory • Wet chemistry laboratory • Instrumental laboratory • Microbiology laboratory • Stability testing • Retention samples storage • Laboratory materials management
Afternoon	Documentation review, such as: • Master documents • System for record keeping • Calibration, qualification and validation procedures and schedules • Maintenance procedures • Batch record review • Specifications, testing and release/rejection procedures for materials and products • Sanitation and hygiene program • Complaint handling procedure • Product recall procedure • Change control • Out of specification/Out of trend procedures • Handling of deviations • Job descriptions • Personnel training • Personnel hygiene • Product quality review • Self-inspections • Corrective and preventive action (CAPA) procedures • Rework/Reprocessing procedure • Quality risk management • Review of additional documents
	Wrap up and summary of findings / Closing Meeting

APPENDIX III: GUIDANCE FOR RATING OF "SITE" AND "QMS" COMPLIANCE RISKS

Indicator criteria have been defined in order to increase transparency when rating the compliance risks associated with "Site" and "Quality Management System" ("QMS") of the FPP manufacturers assessed. A score of "3" represents a high compliance risk, whereas a score of "1" represents a low compliance risk.

Table 1: Indicators for score criteria for site.

Prerequisite	Rating		
	1	2	3
Premises	Premises are designed to be suitable for pharmaceutical manufacturing	Premises show significant deficiencies from WHO GMP but do not impair production safety	Premises are unsuitable for pharmaceutical manufacturing → Production safety impaired
Utility	Utilities which have direct product contact (e.g. Water, Air Handling, Compressed Dried Air) are in place as required, suitable and effective/ functioning	Utilities which have direct product contact (e.g. Water, Air Handling, Compressed Dried Air) are in place as required but not fully compliant with WHO GMP	Utilities which have direct product contact (e.g. Water, Air Handling, Compressed Dried Air) are not available although required, or available utilities are unsuitable
Equipment	Equipment for all manufacturing steps and quality controls are suitable to perform the operation and functioning	Equipment for at least critical manufacturing steps and quality controls are in place and suitable to perform the operation and functioning	Equipment for critical manufacturing steps and quality controls are not available or not functioning

When assigning the overall site rating, the rating (1, 2 or 3) which most reflects the various individual ratings that were assigned to the site attributes should be chosen.

Table 2: Indicators for score criteria for QMS.

Prerequisite	Rating		
	1	2	3
GMP documentation and procedures	A systematic holistic approach towards GMP documentation is in place; procedures performed are adequate and based on a documented system	No systematic approach towards a documentation system is in place; sporadic implementation of GMP requirements; procedures performed are not always based on a documented system	No GMP documentation is in place; procedures are totally inadequate
Calibration/Qualification/ Validation	A systematic approach based on master documents, schedules, protocols and reports is in place	Checks for performance of critical equipment, instruments and methods done but not to an extend required and/or not based on a systematic approach	No calibration, qualification, validation are performed
Preventive Maintenance	Comprehensive preventive maintenance procedures based on a systematic approach are in place	Preventive Maintenance for critical systems is performed but no systematic approach including schedules, protocols, reports/logs are in place	No preventive maintenance is performed
Sanitation	Cleaning is adequate; a systematic approach to cleaning consisting of validation, cleaning schedules, logs are in place	No signs of inadequate cleaning are observed, but no systematic approach to cleaning including cleaning validation, schedules, logs is in place	Evidence of widespread accumulation of residues/extraneous matter exists; evidence of gross infestation is observed

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