GHANA
GMP ROADMAP

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

Produced as part of an ECOWAS regional initiative

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2019

ACKOWLEDGMENT

This document is an updated version of the Ghana GMP roadmap that was developed in 2015. Both the original and the update have been prepared by Kay Weyer (Lead GMP Expert), with Martin Nicholson (International Pharmaceutical Expert).coordinating the work along supported by Louis Nortey. Overall guidance has been provided by Alastair West (UNIDO's PMPA Business Plan Coordinator). Technical inputs have also been provided by Sue Mann and Arie Matt. It has been developed and updated in close collaboration with representatives from the FDA including Seth Seaneke, Samuel Asante- Boateng, Francis Kennedy Amoni, and Mercy A. Owusu-Asante, under the leadership of the CEO, Delese A.A. Darko.

The initial roadmap was developed under UNIDO's Global project on strengthening the pharmaceutical industry in developing and least developed countries to contribute to improved access to essential medicines. This project also covered the broader assessment of Ghanaian companies during 2016. The West African Health Organization (WAHO) has supported a regional project which has enabled the continuation of this work including provision of technical guidance to Ghanaian manufacturers and for the incorporation of the Ghana roadmap approach into an ECOWAS GMP roadmap framework. Carlos Brito and Sybil Ossei Agyeman Yeboah have been the main representatives from WAHO.

CONTENTS

ACRONYMS

CAPA	Corrective and Preventive Action Plan
CDA	Compressed Dried Air
EDAIF	Export Development and Agricultural Investment Fund
ETLS	ECOWAS Trade Liberalization Scheme
FDA	Food and Drugs Authority
GMP	Good Manufacturing Practice
HVAC	Heating Ventilation Air Conditioning
IPA	Investment Promotion Agency
IQ	Installation Qualification
MOF	Ministry of Finance
MOH	Ministry of Health
MOTI	Ministry of Trade and Industry
NDPC	National Development Planning Commission
OOS	Out of Specification
OOT	Out of Trend Results
OQ	Operational Qualification
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection
PMAG	Pharmaceutical Manufacturers Association of Ghana
PMPA	Pharmaceutical Manufacturing Plan of Action
PQ	Performance Qualification
QMS	Quality Management System
SOPs	Standard Operating Procedures
TRS	Technical Report Series
USP	United States Pharmacopeia
UNIDO	United Nations Industrial Development Organization
WAHO	West African Health Authority
WHO	World Health Organization

I. INTRODUCTION

This document presents a Good Manufacturing Practice (GMP) Roadmap for the Ghanaian pharmaceutical manufacturing industry. It has been developed in close collaboration with the Food and Drug Authority (FDA) and in conjunction with the Pharmaceutical Manufacturers Association of Ghana (PMAG). The Roadmap provides a technical basis for developing the country's pharmaceutical manufacturing industry, which under Ghana's Long Term Development Plan (LTDP), has been identified as a priority sector.

The first iteration of the Ghana GMP Roadmap was developed in 2015, when it was validated by national stakeholders. This document is an updated version of the original document and includes the same technical components as well as reference to the Regional GMP Roadmap Framework that has since been developed for West Africa. It also includes an addendum (Annex B) describing the progress that has been made since 2015.

Ghana has the second largest pharmaceutical manufacturing sector in the ECOWAS Region with 38 manufacturers registered with the FDA and over 30 actively producing, directly employing over 5,000 people. The companies are all members of PMAG which provides, inter alia, strong lobbying on behalf of the industry. However, the industry faces significant challenges if it is to grow its share of the national market and significantly expand the exports of pharmaceutical products from Ghana. This has been recognized by a number of Government and parastatal entities which have instituted policies and legislation to support or protect the national industry. These include the establishment of a restricted list which covers products that contain 49 active pharmaceutical ingredients by the FDA, expedited registration for locally manufactured products, and the adoption of procurement preferences for local manufacturers of 15% by the Ministry of Health (though this is allegedly not consistently applied).

Estimates of the size of the market and the proportion that is accounted for by local manufacturers vary significantly as do estimates of the value of exports. A commonly quoted figure is that imports make up 70% of the pharmaceutical market. Reliable export figures are not available, but these are not thought to be particularly substantial. The industry is constrained in part by the limited product categories that companies operate in, focusing on over the counter medicines, basic antibiotics, anti-malarials and anti-helminths in particular; as well as the defragmented nature of the most accessible potential export markets, the Member States of the ECOWAS region. No companies in Ghana have WHO prequalified products and therefore are not able to compete in the international donor funded market for core products to treat for example HIV, TB and malaria.

The FDA is a relatively strong national medicines regulatory authority that has continually developed all the functions required by a National Medicine Regulatory Authority. For example it has a well-regarded quality control laboratory and is working closely with WHO to reach prequalification. However, it still faces significant challenges in assuring the quality of products on the market and limiting the prevalence of sub-standard and falsified medicines.

The priority status of the sector in Ghana and the initiatives that have been taken to date are consistent with the ambition to strengthen the industry in Africa, as has been articulated at the continental level through the Pharmaceutical Manufacturing Plan for Africa and in West Africa, through the ECOWAS Regional Pharmaceutical Plan (ERPP). These and other initiatives recognise that strengthening the pharmaceutical manufacturing industry can contribute to improved access to safe,

effective, affordable medicines. Impacts can be achieved through 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 developments could also drive an increase in trade within the region, the continent and 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 Ghana and could be an important component in reducing the country's reliance on imports as well as increasing exports.

Therefore, ambitions to develop the pharmaceutical industry in Africa have been established, and it has been identified as a priority sector in Ghana. With one of the continents larger pharmaceutical sectors, the country 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 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 Corrective Action and Preventative Action (CAPA) plans. To

ensure that manufacturers are making the requisite progress in implementing these company level plans, the site level developments can be monitored by the FDA.

This roadmap is focused on the strengthening of the pharmaceutical industry in Ghana. The initial version was developed with support from UNIDO under its global project for strengthening the local pharmaceutical industry in developing and least developed countries. Initial assessments of seven manufacturers that were identified using the sampling methodology described in this document were conducted. The results were analysed to provide a baseline of existing levels of compliance with GMP and the key technical challenges that pose most threat to production safety are prioritised in the stepwise, risk based approach for upgrading the industry.

As detailed in the addendum, 26 manufacturers were assessed in 2016, and the findings demonstrated the validity of the original results, with the broader sample also highlighting exactly the same key technical challenges.

In 2017 the West African Health Organization and UNIDO began a collaboration 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 across the region, 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. Such a regional Framework was developed based on the same methodology used for this roadmap. It was validated at a regional workshop held in Abidjan in November 2018 and will form the central component of a comprehensive programme to support the strengthening of the industry across the region and at the level of individual ECOWAS Member States.

Thus, strengthening of the pharmaceutical industry in Ghana can be overseen by the FDA, implemented by PMAG and its members 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 GHANA GMP ROADMAP TOWARDS WHO GMP

1 Fundamental principles of GMP and the overarching considerations for developing a Roadmap

Adherence to 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 in Ghana are often overwhelmed by the vast array of GMP requirements, making it difficult for them to operate in line with internationally accepted GMP standards. The GMP standard referred to in this context and which is the one that is the reference point for this document is that which has been defined by the World Health Organization (WHO)[1] and is therefore internationally recognised.

In order to support Ghanaian companies in their progress towards internationally recognised 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. The Roadmap development has been tailored to the specific situation in Ghana and built on a baseline assessment of Ghanaian pharmaceutical manufacturers in terms of their level of compliance with WHO GMP. In this context, a tool for risk categorisation of companies, according to their compliance with WHO GMP, has also been developed.

The resulting Ghana GMP Roadmap will be used as a stepwise tool to guide companies and regulatory authorities on the path towards WHO GMP compliance. Companies 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[2]. New start-up companies can use the Roadmap 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 will also enable the Ghana Food and Drugs Authority to review licensing criteria for new and existing facilities in order to ensure alignment with WHO GMP requirements.

Since the initial GMP roadmap for Ghana was developed and endorsed in 2015, the multiple dimensions that need to be addressed to enable manufacturers and other stakeholders to fully implement the roadmap and strengthen the industry more generally have been the subject of detailed discussions amongst key stakeholders. This has been part of a process to develop a detailed strategy for strengthening the sector, with the upgrading approach articulated in this document being a key pillar. Furthermore, through a combination of support from the Global Project and the

[1] "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 961, Annex 3 and TRS 986, Annex 2.

[2] It should be noted that since the development of this roadmap (based on a representative sample of 7 companies), 26 companies have been assessed in Ghana through the collaboration between the FDA and UNIDO which has also supported them to develop CAPA plans. This progress has been supported through the WAHO Regional GMP Roadmap framework project and the UNIDO Global Project.

initiative with the West African Health Organisation (WAHO) significant progress has been made from a technical perspective as elaborated in the Addendum to this document (see Annex B).

2 Objectives

In order to develop a pathway towards compliance with WHO GMP tailored to the specific situation in Ghana, the following activities were undertaken:

- Baseline assessment of existing manufacturing practices in the Ghanaian pharmaceutical industry, in order to evaluate the level of compliance with WHO GMP across the range of pharmaceutical companies in Ghana, 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 Ghana GMP Roadmap needed to delineate a risk-based, phased approach towards compliance with WHO GMP tailored to the specific situation in Ghana.
- Definition of key aspects and tools for the implementation of the Ghana GMP Roadmap

3 Scope

This document focuses on the WHO GMP requirements for the manufacture of:

- **Non – sterile and sterile dosage forms**
- **Medicinal products containing small molecular entities** that are active substances with a molecular weight of not more than 800 g/mol. To date, most active substances are small molecular entities.

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

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

4.1. Approach

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

1. Development of tools for assessment of Ghanaian pharmaceutical manufacturers and their evaluation regarding compliance with WHO GMP
2. Selection of companies for assessment
3. Assessments at selected companies
4. Evaluation of results gathered during assessments

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

The focus of the baseline assessment was on companies with different levels of compliance to WHO GMP. The intention was to reflect the entire compliance range found among Ghanaian pharmaceutical manufacturers. Several pharmaceutical companies 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 companies. This methodological groundwork comprised the following activities:

- Selection of a GMP reference standard for assessment of companies
- 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 companies

The internationally recognized GMP standard used as reference for the assessment of pharmaceutical manufacturers in Ghana 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 961, Annex 3 and 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 Ghana 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 companies involved. Each company 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, 25 May 2012, EMA/INS/GMP/321252/2012 Rev 14). The assessments were performed during November and December, 2012, and the deficiencies were classified as follows:

Critical Deficiency:

A deficiency which has produced, or leads to a significant risk of producing either a product which is harmful to the human or veterinary patient or a product which could result in a harmful residue in a food producing animal.

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 Ghanaian pharmaceutical manufacturers with WHO GMP, and to identify main technical challenges across the range of pharmaceutical companies in Ghana, two tools have been developed:

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

Tool 2: Categorization of companies 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 companies, and to identify those key quality elements to which highest and lowest compliance was observed, respectively. Using the plain ratings of individual observations made during each company assessment would not have been suitable due to the variety of individual observations. Therefore, based on the rating of observations made during the company assessments, a rating of the compliance of key quality elements with WHO GMP was derived. The approach allowed observations that were related to a specific key quality element to be rated as a whole, reflecting the overall compliance of the respective key quality element with WHO GMP requirements. These 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 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 company.

This rating key fulfilled the aforementioned requirement to compare company performances, and to identify those key quality elements to which highest and lowest compliance were observed. In this way the main technical challenges leading to WHO GMP non-compliance could be identified. The rating key is a useful tool to evaluate particular weaknesses in compliance displayed by different local pharmaceutical manufacturers.

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

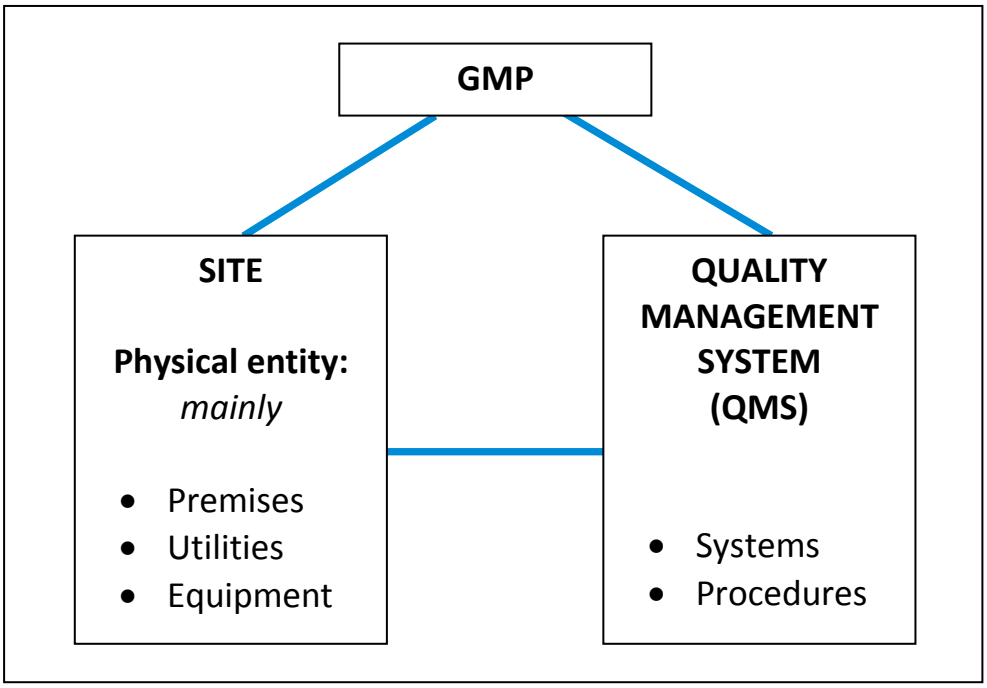
Tool 2: Categorization of companies based on their compliance with WHO GMP

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 Ghana. The spectrum ranges from companies 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 compliant 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 company 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 companies 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).

Risk levels of "1", "2" or "3" were assigned to both site and quality management system to describe their compliance with WHO GMP, with a risk level of "3" representing a high compliance risk, and a risk level of "1" representing a low compliance risk.

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

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

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

4.3. Selection of companies for assessment

The focus of the baseline assessment was on pharmaceutical manufacturers at different levels of compliance with WHO GMP and in need of guidance to achieve full WHO GMP compliance. The participation of companies in this project was on a voluntary basis.

Eligible for inclusion in the assessment were pharmaceutical manufacturers that

1. had not yet achieved full compliance with WHO GMP,
2. represented the different levels of GMP compliance to be found in the Ghanaian private sector, and
3. gave their consent to participate in the assessment.

An initial screening of companies to determine eligibility according to the above selection criteria was conducted based on the paper "Assessment of local Pharmaceutical Companies on GMP Compliance and the Development of the Roadmap, 2010" prepared by the Ghanaian Food and Drugs Authority (FDA). This paper provided a rating of Ghanaian pharmaceutical manufacturers according to their GMP compliance in terms of the following scheme: "A" (highest GMP compliance), "B" (good GMP compliance), "C" (moderate GMP compliance), "D" (borderline GMP compliance), "E" (below borderline) and "sub" (lowest GMP compliance). Pharmaceutical manufacturers encompassing a range of GMP compliance from class "A" (highest GMP compliance) to class D (borderline GMP compliance) were selected for the assessment. Companies with a rating of "E" (below borderline) and "sub" (lowest GMP compliance) were not included in the assessment due to the high number of deficiencies already observed for companies rated "D".

For the assessment, 7 companies were selected based on the rating scheme provided by the Ghanaian FDA ranging from "A" to "D" as follows:

- 1 company rated “A” (highest GMP compliance)
- 3 companies rated “B” (good GMP compliance)
- 2 companies rated “C” (moderate GMP compliance)
- 1 company rated “D” (borderline GMP compliance)

4.4. Assessment results and evaluation

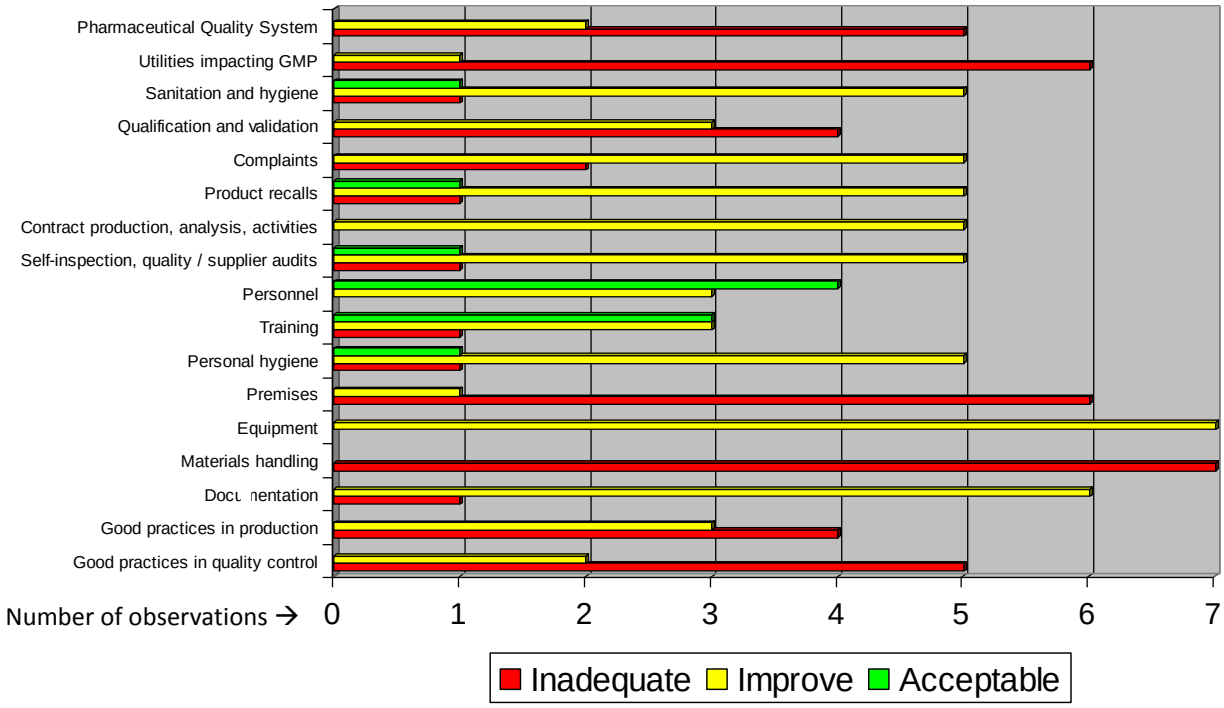
The company assessments were performed in 2012[3], using the criteria as described in section 4.3. During the assessments, seven companies were reviewed regarding their compliance with WHO GMP. The results gathered during the assessments have been anonymized:

- No company names or details which would allow tracing of participants are presented;
- The sequence of companies presented is randomised and does not represent the sequence of their assessment.

4.4.1. Compliance of participating companies to key quality elements of WHO GMP

The results regarding compliance of participating companies to key quality elements of WHO GMP are shown in figure 3.

Figure 3: Overview of compliance of participating companies to individual key quality elements of GMP



The results above show that the compliance of the vast majority of key quality elements with WHO GMP needed improvement or were inadequate. Although companies participating in the assessment were very interested in upgrading their GMP compliance, the number and severity of observations indicated that there was limited awareness of WHO GMP requirements, within both the

[3] See addendum for analysis comparing findings from 2012 with results from assessments in 2016 (providing a total cohort of 26 assessed companies) which underscores the validity of the findings in this document.

pharmaceutical industry and the regulatory authority that had licensed the participating companies for manufacturing and hence had certified them for GMP compliance. This indicated a need for training not only of pharmaceutical manufacturers but also of the regulatory authority to reinforce understanding of WHO GMP requirements, and to ensure that GMP compliance of Ghanaian companies would be monitored appropriately. Since the first iteration of the Ghana Roadmap significant formal and informal awareness raising and training for industry stakeholders and FDA experts has taken place both as part of the UNIDO work (see Addendum) and through other initiatives undertaken, inter alia, by the FDA.

Despite the high number of quality elements which were either rated “inadequate” or “improve”, the scientific degrees held by company personnel was, for the majority of companies, adequate. 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 their insufficient knowledge of WHO GMP requirements on the other potentially reflects a generalised problem with existing educational systems, which may warrant review of academic and post-academic curricula, and highlights the need for continuous training of staff working in pharmaceutical companies or the regulatory authority. However, this is another area where substantial progress has been made since the first iteration of this document, with for example, a number of universities introducing industrial pharmacy modules to their pharmacy undergraduate curricula.

Figure 3 reveals that the key quality elements with the least GMP compliance and hence with the most frequent occurrence of the rating “inadequate” are:

- Utilities impacting GMP
- Premises
- Materials

Utilities and premises relate directly to the structural constituent of GMP and hence impact directly on the compliance of the site with WHO GMP. Serious observations regarding “Material handling” included deficiencies regarding facilities for material handling as well as deficiencies due to inadequate quality management systems (QMS).

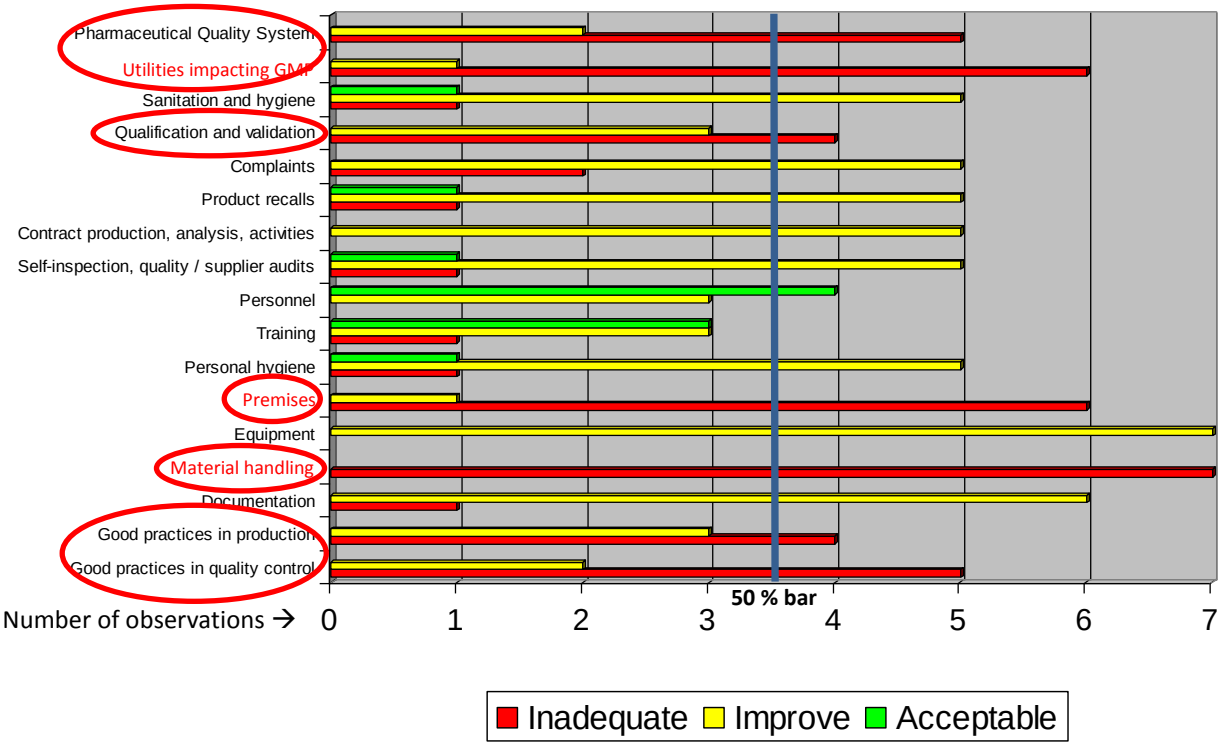
The high number of “inadequate” ratings for the key elements “Utilities impacting GMP” and “Premises” is directly related to the site, and the high number of “inadequate” ratings for the key element “Materials” is caused by serious deficiencies regarding both components of GMP, namely site and QMS. These facts indicate that a main challenge for WHO GMP compliance in Ghana is the lack of GMP compliant sites. Consequently, a high need has been identified for provision of guidance to manufacturers on site design requirements. Due to the high number of serious deficiencies related to site issues, and given that site related modifications are generally difficult and quite costly, it is clear that the Roadmap towards WHO GMP requires a strong initial focus on improvement of site related GMP aspects.

Additional key quality elements for which the majority of companies showed inadequate compliance are:

- Pharmaceutical quality system
- Qualification and validation
- Good practices in production
- Good practices in quality control

Figure 4 provides an overview of key quality elements for which the highest number of companies showed least compliance and for which the majority of companies showed inadequate compliance.

Figure 4: Overview of compliance of participating companies to individual key quality elements of GMP: prioritisation of Key Quality Elements based on compliance level analysis



The seven key quality elements circled in red indicate those for which the majority of companies showed inadequate compliance. Of these, the three elements highlighted in red font are those for which the highest number of companies showed least compliance.

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

- Pharmaceutical Quality System
- Utilities impacting Good Manufacturing Practice (GMP)
- Qualification and validation
- Premises
- Materials
- Good practices in production
- Good practices in quality control

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

Companies 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 companies based on their compliance with WHO GMP are shown in table 2.

Table 2: Results of company categorization based on their compliance with WHO GMP

Company name	*Risk Level Site*	*Risk Level QMS*	*Overall GMP rating*
Company 1	2	1	B
Company 2	3 (a very small independent line was rated 2)	2	C ("B" for the very small independent line)
Company 3	3	2	C
Company 4	3	2	C
Company 5	3	2	C
Company 6	3	3	C
Company 7	3	3	C

The categorization shows that out of the seven companies assessed only one manufacturer received an overall GMP rating of "B" (medium risk company) for the entire company, and another manufacturer received a "B" rating only for a very small independent manufacturing line, whereas the other major lines of the company were rated "C" (high risk company). The remaining companies were assigned an overall GMP rating of "C" (high risk company). The risk level for compliance of QMS with WHO GMP requirements ranged from "1" to "3", whilst the risk level for compliance of site with WHO GMP requirements ranged from "2" to "3". This result verifies that the selection of companies was suitable for the assessment, as the selection criteria were designed to define only companies that have not yet achieved full compliance with WHO GMP (no company 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 companies assessed received an overall "C" rating. This rating showed that the existing approaches towards pharmaceutical manufacturing were not in line with WHO GMP and that a high risk existed with regard to production safety.

Comparing the risk levels for site and QMS reveals that the risk associated with site was usually higher than that caused by QMS. The compliance risk regarding QMS was rated with a risk score of "2" for the majority of companies (4 out of 7 companies), meaning that QMS are implemented sporadically. One company achieved a risk level of "1" reflecting that a systematic approach towards a QMS in line with WHO GMP requirements was in place. Two companies had no QMS in place (risk level of "3").

Whereas 5 out of 7 companies attained a QMS related risk level of "2" or better, the vast majority of companies (6 out of 7 companies) received a site related risk level of "3" for at least the major parts of their sites. These results reflected that the vast majority of existing sites are impairing production

safety and were therefore not suitable for pharmaceutical manufacturing. Only one company and a small independent manufacturing line of a second manufacturer attained a site related risk level of "2", meaning that significant deficiencies regarding WHO GMP exist but that production safety is not impaired.

The results of the risk assessments - that the high compliance risk associated with site is a major reason for low compliance with WHO GMP - underlines the observation made in view of the compliance rating of the key quality elements, which showed that "inadequate" ratings were more frequently identified for key quality elements that are directly or at least partly associated with site.

The fact that site related observations were the main reason for lowering the overall GMP rating clearly indicated that strong guidance was needed regarding site related GMP aspects and design requirements. Based on the outcome of the assessments, site related GMP aspects needed to be one of the key aspects during the design of the GMP Roadmap. Nevertheless, it has to be pointed out in this context that, although the compliance risks regarding QMS were lower than those associated with site, 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, due consideration needs to be given to the fact that the construction of new, WHO GMP compliant sites, or modification of existing manufacturing sites is time consuming and costly. On the other hand, 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 companies in Ghana:

- 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 Ghana GMP Roadmap.

5 Components of the Ghana GMP Roadmap

The design of the Ghana GMP Roadmap document takes into account the outcomes of the baseline assessment of Ghanaian pharmaceutical manufacturers conducted in 2012[4] with regard to their existing level of compliance with WHO GMP (as described in section 4 of this document).

[4] The results from assessment of 26 companies in 2016 attested to the veracity of the methodology described herein (see Annex B).

The Roadmap delineates a phased approach to WHO GMP compliance and sets out requirements and milestones for pharmaceutical manufacturers to be achieved during the progression of these companies 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, the approach to the development of this Roadmap was

- 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 Ghana 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 companies showed least compliance.

Although the key quality element “equipment” has not been identified as showing serious deficiencies for the majority of companies, it is among the initial focus items due to its impact on site and qualification.

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

- Pharmaceutical Quality System
- Utilities impacting Good Manufacturing Practice (GMP)
- Qualification and validation
- Premises
- Materials
- Good practices in production
- Good practices in quality control
- Equipment (added in Phase I not due to severity of deficiencies but due to the focus on site)

- Any site related aspects of other key quality elements

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.

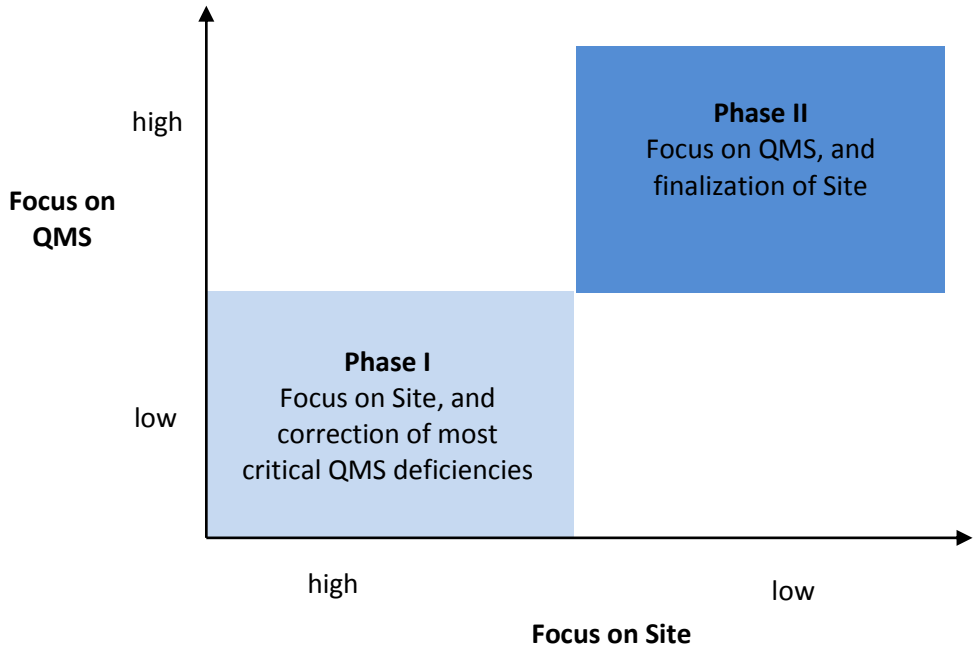
Meanwhile, it is acknowledged that, depending on the extent of work required to establish WHO GMP compliant sites, finalization of construction related activities and/or site related documentation which has not been finalized during phase I might still be on-going during phase II.

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

- Sanitation and hygiene
- Complaints
- Product recalls
- Contract production and analysis
- Self-inspection and quality audits
- Personnel
- Training
- Personal hygiene
- Documentation

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

Figure 5: Graphic display of focus during the phases of the Ghana GMP Roadmap

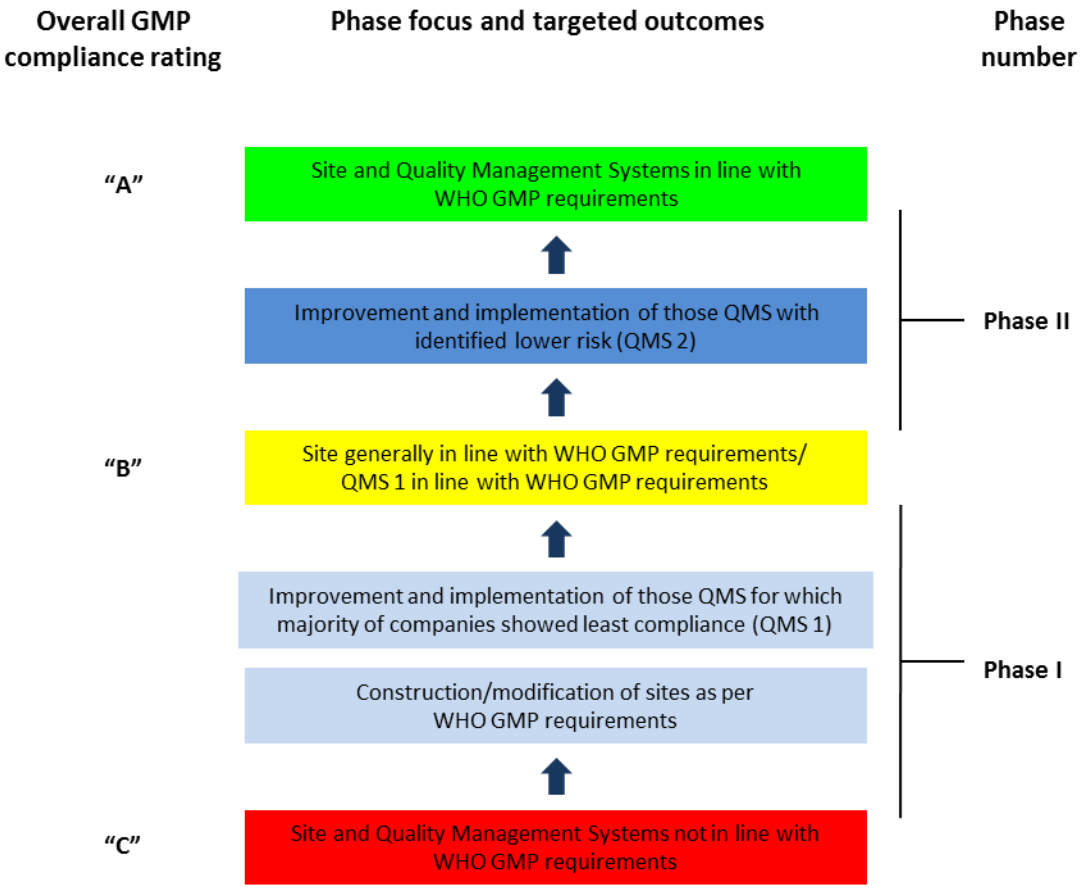


This phased approach allows companies to make stepwise improvements from their existing level of compliance towards full WHO GMP compliance, a pragmatic approach to the complex and time consuming endeavour, particularly where substantial discrepancies exist.. Analysis of the risk assessment of the companies (refer to section 4.4.2) revealed that the majority of pharmaceutical manufacturers were rated as class “C”, meaning “high risk companies”, mainly due to the high risk associated with their sites.

Therefore, Phase I focuses on the establishment of WHO GMP compliant sites and on those quality management systems which showed most severe deviations from WHO GMP. Using the results of the risk assessment, the majority of currently class "C" rated companies following the phased Roadmap approach should reach a "B" rating at the end of phase I, as their sites, which were the predominant 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 companies showed least compliance will also be in line with WHO GMP requirements at the end of phase I, enabling companies 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 GMP and hence the companies will be operating in line with WHO GMP.

This stepwise approach towards full WHO GMP compliance is graphically displayed in figure 6. As the definition of the individual phases of the GMP Roadmap is done based on the severity of deviations from WHO GMP and on the compliance risk observed at Ghanaian pharmaceutical manufacturers, a stepwise, risk-based approach could be realized for development of the Ghanaian roadmap towards achievement of full WHO GMP compliance.

Figure 6: Stepwise approach towards achievement of full WHO GMP compliance, using the risk-based, phased approach of the Ghana GMP Roadmap



Based on the results obtained from the WHO GMP compliance assessment of the Ghanaian 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 Ghana GMP Roadmap presents for each GMP relevant aspect:

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

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

5.3 Utilization of the Roadmap

The Ghana GMP Roadmap has been developed based on the results from on-site assessments of Ghanaian pharmaceutical manufacturers and has been tailored to the specific situation in Ghana. 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 961, Annex 3 and 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 the respective WHO GMP guidelines. The Roadmap should be used as a stepwise tool to guide companies and regulatory authorities on the path towards WHO GMP:

- Already **existing companies** 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 company, 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. The targeted timeframe for the entire project should be 5 years, with

- The first phase targeted to take no longer than 3 years, and
- The second phase targeted to be completed within 2 years.

However, as has been seen, many other factors affect the ability of companies and related associated stakeholders to implement the roadmap. Under this revised roadmap, specific deadlines for achieving the established milestones (B rating then A rating) in the context of these broader considerations will be determined, informed by associated plans to address

these broader issues at the national and regional level (see section III). Distinct years for finalization of phase I and phase II will be determined after consultations amongst ECOWAS Member States to establish the dates by which these key milestones need to be reached. Subject to the specific considerations in Ghana, these deadlines could be brought forward for national manufacturers. It should be noted that the time allocated for phase I is longer due to the need for modification of existing sites or construction of new sites during this phase.

6 Implementation of the Ghana GMP Roadmap

Execution of the Ghana GMP Roadmap requires the development of an implementation plan that takes account of, and therefore includes, multiple strategic components which are required for successful implementation of the Roadmap itself. 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 addressed in the implementation plan will pertain to administrative and governance-related matters, along with technical, financial, incentive-related, human resources related, and advocacy related matters, including:

- 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;
- Training, support and strengthening (as required) of the national regulatory authority with regard to WHO GMP requirements, and overall regulator function;
- 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.

Since the preparation of the initial Ghana GMP Roadmap, deliberation on such matters were central to a detailed, multi stakeholder consultative process to determine a suitable approach for supporting the long term development of the industry in Ghana under the coordination of the National Development and Planning Commission. The consultations to date and the findings therein could form the basis of a national implementation strategy which could be finalised, if required, as the programme to execute the ECOWAS Regional GMP framework is rolled out.

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. Ghana has the second largest pharmaceutical manufacturing sector in the region after Nigeria and the results from the 26 manufacturers that have been assessed 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, international standards being implemented by all manufacturers 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 has taken place across the region.

It is also important to note that upgrading manufacturing standards is a long-term endeavor 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 Ghana 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

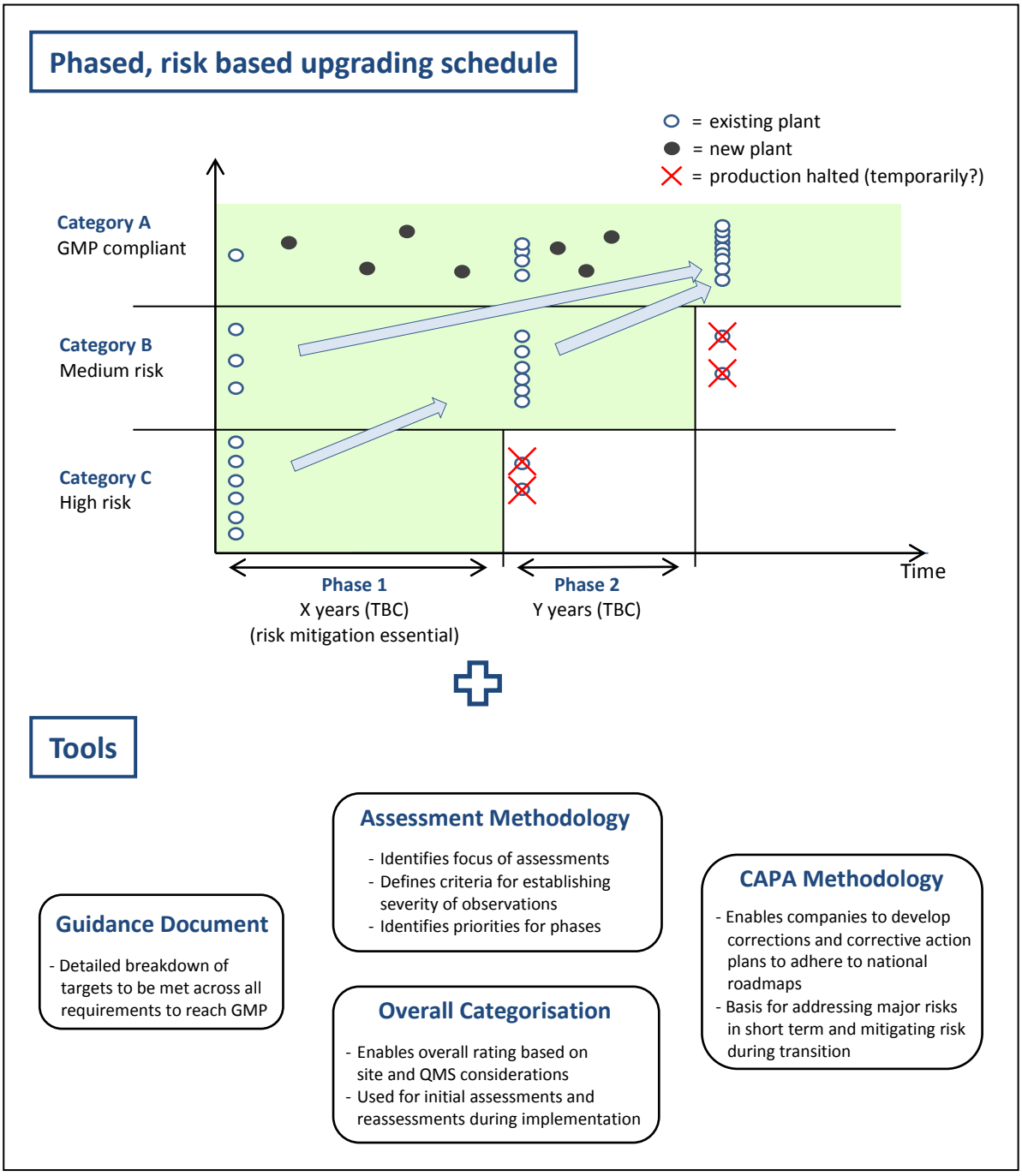
The framework consists of tools (as utilised in the development of the Ghanaian Roadmap) and guidance as well as a risk based phased schedule for upgrading standards. It includes a guidance document that breaks down each of the 17 key quality elements into technical specifics and defines actions and 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 Ghana 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 7: 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 Ghana national roadmap

The Ghana 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 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 Ghana 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 Ghana 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 in close collaboration with the FDA and with strong cooperation from PMAG. The first iteration of the Ghana GMP roadmap was produced in 2015. This document is an updated version of the original. It contains the same technical components as the 2015 document and has been amended to include an addendum (Annex B) that describes progress since the initial roadmap was endorsed by national stakeholders, including for example the results from assessment of 26 companies that were assessed to ascertain their level of compliance with WHO GMP and to identify the key technical challenges that they face. This follow up work has demonstrated the validity of the roadmap's technical components, as the same key technical challenges were identified in the broader sample as were highlighted from the original assessment of a smaller cohort.

The country's pharmaceutical industry has been identified as a priority sector under the Long Term Development Plan that is coordinated by the NDPC. Historically it has received support from a number of national stakeholders, with for example the FDA identifying a restricted list and expediting product approvals for local companies. The Ministry of Health can award tenders to local producers with a 15% marginal price preference compared to imported products. The industry as a whole is also strongly represented by PMAG, which acts as a strong lobbyist for its members needs amongst other services and activities.

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 a recognized international expert 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 the key technical challenges that Ghanaian manufacturers face, regarding 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).

The analysis identified that of the seventeen key quality elements specified in WHO GMP, those with the lowest level of compliance were; Utilities impacting on GMP, Premises and Materials. Pharmaceutical quality system, Qualification and Validation, Good practices in production and Good Practices in Quality Control were also found to be aspects where compliance levels were regularly problematic. A further

finding was that for all companies assessed, the risk level associated with site was worse than or equal to that 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.

The original roadmap included timelines of three years for phase 1 and two years for phase 2. However experience has shown that, whilst in principle this may represent a suitable duration for the transition of manufacturers to internationally recognized standards, in practice the need for a conducive business environment that enables companies to make the requisite investments is a significant factor that is required for such time lines to be met. Therefore specific dates by which companies need to reach these milestones are not included in this document, with further national level consultations required. 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.

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 fifteen ECOWAS Member States, pharmaceutical manufacturers from across the region and their representative bodies such as the West African Pharmaceutical Manufacturers Association, and other stakeholders including the African Development Bank and USP. The methodology applied in this roadmap and the results from the application of the tools are standard for the region. Ensuring consistent calibration of the findings as the framework is implemented will contribute to more transparency and defragmentation of the regional market. This will become increasingly relevant as the sector develops across West Africa and companies progress towards lower risk manufacturing and expanded product portfolios.

This document 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 most 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 that addresses the multiple aspects required to establish a conducive context for pharmaceutical manufacturing in West Africa. The programme will support the development of the industry and, as required, associated stakeholders in Ghana as well as sectors in other countries in the region. In so doing, pharmaceutical manufacturing in Ghana can continue to develop to be commercially viable at internationally recognized standards and the range of products that

are currently manufactured in the country can be expanded. 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 Ghanaians in particular as well as citizens of other ECOWAS Member States.

ANNEX A: GHANA GMP ROADMAP – TECHNICAL SPECIFICS

The technical specifics of the Ghana GMP Roadmap document were developed following a baseline assessment of Ghanaian pharmaceutical manufacturers 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[5] 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 5. 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 (section 1.2);
- **Phase II** focusses 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.

[5] 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 961, Annex 3. 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 • Clean sampling, dispensing and process rooms	Scope of the premises defined.

		• Clean support areas (such as washing, movements and staging)
		• Packaging areas
		• Quality control laboratory
		• Process ancillary areas and equipment
		• Utilities
		
		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 separation 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, including:
		  ○ Separation of quality control laboratories from production areas
		  ○ Separation of rest and refreshment room from manufacturing quality
			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.

		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 • 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	Required water qualities needed for intended operations identified
		Identification of a water source suitable for the production of potable and purified water	Suitable water source (e.g. borehole or public water) identified. Quality of source water identified.
		Definition of (pre-) treatments required of the source water to obtain water of potable and purified quality.	Requirements for water treatment defined.
		Taking into account the quality of the source water, the water qualities to be used within the site and the 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.	Design specifications 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 clean room areas.	Assessment performed.
		Taking into account the environment in which the site is going to be constructed, the product range and activities to be handled within the site and the volumes of the clean room 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 control 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 monitoring/control of functionality of the zone concept and environmental attributes.	Requirements for environmental 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 is 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 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 monitoring of critical attributes such as 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 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.	Design specifications and layout of steam system available. The system has provisions for monitoring of critical attributes.
		Establishment of suitable supplier(s)* for steam system(s).	Suitable supplier(s) identified and contracts available.
		Installation/Commissioning of the steam generation and distribution system(s) complying to the design specifications	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	Equipment	Identification of equipment needs based on product classes to be manufactured, production capacity, operational and control requirements and quality control activities to be performed at the site.	Equipment needs identified.
		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 contact areas, including ○ Type of construction materials ensuring that the materials are not reactive, additive or absorptive or adsorptive ○ Requirements on surface finishes/roughness	Design specifications and layout/drawings of equipment and support systems available.

		• 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 precision of measuring equipments • 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 automization 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 Establishment of suitable supplier(s)* for equipment. Installation/Commissioning of equipment complying to the design specifications	Suitable supplier(s) identified and contracts available Equipment complying with predefined specifications and design in place. As-built equipment conforms to original design drawings.
1.1.4	Personnel/ Personal	Based on product range, operational steps and production capacity define the number	Number and qualification of

	hygiene	and qualification of personnel required. Taking into consideration the product range, 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.	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.

1.1.5	Materials	Taking into consideration the targeted production output 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 on environment, required monitoring devices, cleanability, space and security in order 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 procedures 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.	Design specifications and layout for storage and material transport are in place. Areas complying with original specifications and design
1.1.6	Gd practices in production	(covered in section 1.1.1: Premises)	(covered in section 1.1.1: Premises)

1.1.7	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 sampling, inspecting, testing 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 • 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	Analytical activities defined Design specifications and layout for premises and equipment are suitable for performance of quality control activities.

		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
END OF SECTION: PHASE I, SITE			

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 qualify, 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	Utilities impacting Good Manufacturing	Development and implementation of a system containing documented procedures, protocols, reports and records for calibration, qualification, maintenance	System containing documented procedures, protocols, reports and records for

	Practice	and cleaning and sanitization for each equipment	calibration, qualification, maintenance and cleaning and sanitization for each equipment in place and implemented
		Development and implementation of documented procedures for operation of equipment 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 and 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
1.2.3	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, 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	Plans, protocols and reports for (re)-calibration, (re-) qualification and (re-)

		procedures, plans and reports for (re-)calibration, (re-)qualification and (re-)validation of building, utilities, equipment, controls, processes and methods as outlined in the validation master plan Development and implementation of systems for review and tracking of calibration, qualification and validation status	validation in place as outlined in the Validation Master plan and implemented Systems for review and tracking of calibration, qualification and validation status in place and implemented
1.2.4	Premises	Development and implementation of a documentation system containing procedures, protocols, reports and records for qualification, maintenance and cleaning, sanitization of premises 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 Furthermore, the pest control program has to ensure suitability of substances used for pest control according to their areas of use. Development of a system defining the room status (e.g. clean, in operation, awaiting cleaning, under maintenance) within operational sections	Documentation system for qualification, maintenance, cleaning and sanitization of premises in place and implemented Documented program for pest control including procedures for contractors in place and implemented Documented system for defining room status in place and implemented
1.2.5	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. Development and implementation of documented procedures for handling of defect equipment and support systems.	Documented system for defining equipment status in place and implemented. Documented procedures for handling of defect equipment and support systems in place and implemented.
1.2.6	Materials	Development and implementation of documented systems and procedures for receipt, handling, sampling, inspecting, release, rejection, 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 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	Documented systems for receipt, handling, sampling, testing, release, rejection, distribution and destruction of materials, labels, intermediates and finished products in place and implemented

		personnel for access and status change • Development and implementation of a system for unique identification of materials, labels, intermediates and products including identification code, 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 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 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	Good practices in production	Development of a system to identify and classify substances handled regarding their potency, hazardous or sensitizing potential and the derivation of containment requirements based on the classification done	System to identify and classify substances handled regarding their potency, hazardous or sensitizing potential and the derivation of containment requirements based on the classification in place and implemented

		Development and implementation of organizational procedures to avoid contamination and cross-contamination, ensuring containment to the extent required and 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	Organizational procedures to avoid contamination and cross-contamination, and ensuring containment to the extent required is 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 allowing full traceability of batch history	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
1.2.8	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 are available at the required quality	System ensuring that all required reference standards, reagents/solvents and culture media are available at the required quality is 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	Procedures, records and logs for handling of reagents/solvents, culture media including required quality, identification of suppliers, receipt,

		reagents and culture media, procedures for standardization and suitability testing where appropriate	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 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 working reference 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 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	Stability programs in place and implemented

		WHO/ICH requirements Development and implementation of a system for drawing, handling, storage and inspection of retention samples. Definition and implementation of appropriate garment and safety procedures for protection of operator and environment and to avoid any contamination of samples Development and implementation of procedures for waste handling	in line with WHO/ICH requirements System for drawing, handling, storage and inspection of retention samples in place and implemented Appropriate garment and safety procedures in place and implemented 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 Ghana 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. Development of an environmental monitoring program including specifications, action and alert limits, sampling procedures and frequencies evaluation.	A comprehensive cleaning program including schedule and logs is in place and followed. Environmental monitoring programs are developed and implemented.
2.2	Complaints	Development and implementation of a documented system regarding handling, investigation, corrective and preventive actions of complaints containing: • Responsible person(s) and responsibilities • Procedures to be followed for handling, investigation, corrective and preventive 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	Documented 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 and corrective and preventive actions • The need to extend investigation to other batches, materials, products • Reconciliation of recall • Registration 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 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 and/or analysis is done. Development and implementation of documented procedures to ensure that contract production and analysis is performed in accordance to the marketing authorization of the product and in line with GMP requirements containing: • Pre-requisites to be fulfilled before contract production/analysis takes place including evaluation of potential contract acceptor regarding legality, suitability and competence • Written agreements between	Needs for contract production/analysis identified Documented procedures for contract production/analysis in place and implemented

		contract giver and acceptor detailing responsibilities, knowledge management, attributes impacting quality of product/service, release and documentation procedures, access of the contract giver to records and raw data, continuous re-evaluation of contract acceptor and sub-contractors where needed • List of approved contract organizations	
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 • Corrective and preventive 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 suppliers; 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	Self-inspection procedures developed and implemented Procedures for manufacturer and supplier qualification in place and implemented

		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 of materials • Procedure, criteria and periods for monitoring and re-evaluation/re-qualification of manufacturers and suppliers of starting and packaging materials	
2.6	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
2.7	Training	Development and implementation of documented training procedures including: • Training needs assessment • Training program for induction, on-job and continuous 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 procedures in place and implemented

		• Training records including their review and update procedures • Training requirements for external support staff/contractors	
2.8	Personal hygiene	Development and implementation of documented procedures to ensure GMP-conform personal hygiene 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	Documented procedures ensuring GMP-conform personal hygiene in place and implemented

		smoking material and personal medicines in production, quality control areas and warehouse areas • Training programs on personal hygiene	
2.9	Documentation	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	Comprehensive documentation system in place and implemented

		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 company procedures, forms and current version numbers allowing traceability of revision history • 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	
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.

ANNEX B: ADDENDUM – RELEVANT TECHNICAL DEVELOPMENTS SINCE INITIAL ENDORSEMENT OF THE GHANA GMP ROADMAP

This addendum provides an overview of technical developments relevant to the implementation of the Ghana GMP Roadmap after its endorsement by Ghanaian stakeholders in 2015. This addendum has been prepared in May 2019.

The following key technical activities for implementation of the Ghana GMP Roadmap and for provision of a regional context for the Ghana GMP Roadmap were conducted in the period 2016 to May 2019:

1. Assessment of Ghanaian manufacturers of finished pharmaceutical products
2. Technical assistance on CAPA preparation and CAPA review
3. Development of the Regional GMP Roadmap Framework for the ECOWAS Pharmaceutical Manufacturing Industry

1) Assessment of Ghanaian manufacturers of finished pharmaceutical products

As part of the implementation of the Ghana GMP Roadmap 26 Ghanaian FPP manufacturers were assessed in 2016 by assessment teams led by UNIDO GMP Experts in collaboration with the Ghana FDA. The objectives of these assessments were:

- Provision of technical assistance to Ghanaian pharmaceutical manufacturers through identification of gaps between current levels of manufacturing and WHO GMP requirements
- Strengthening of regulatory capacity through the provision of technical assistance to the regulator during the gap analysis of pharmaceutical manufacturers in the form of hands-on capacity development regarding WHO GMP requirements, during assessments of FPP manufacturers and CAPA review

Details of the assessment process were delineated in an Aide Memoir document outlining technical specifics as well as communication process, timelines, responsibilities and ground rules for the various parties involved in this project.

The assessments included besides FPP manufacturers and FDA inspectors from Greater Accra also manufacturers and inspectors from Kumasi and Koforidua, ensuring that manufacturers and inspectors from various areas of Ghana received technical assistance.

The outcomes of the GMP assessment performed in 2016 were compared with the results of the baseline assessment performed for development of the GMP Roadmap.

Therefore, it was evaluated whether conclusions made for the development of the Ghana GMP Roadmap based on the baseline assessment could be verified after the GMP assessments made in 2016.

As one part of this comparison the main technical challenges identified during the baseline assessment regarding the key quality elements were compared with outcomes of the 2016 assessment.

The key quality elements for which “critical” deficiencies had been observed during the assessment of the 26 FPP manufacturers in 2016 and hence resulted in “inadequate” compliance of these key quality

elements with WHO GMP are stated in table 1. This table also displays the number of manufacturers for which "critical" deficiencies were observed for the various key quality elements.

Table 1: Number of manufacturers with "critical" deficiencies for the various key quality elements

Key quality element	Number of manufacturers for which one or more critical deficiencies were observed regarding the key quality element
Pharmaceutical Quality System	13
Utilities impacting Good Manufacturing Practice (GMP)	26
Qualification and validation	23
Premises	24
Material handling	24
Good practices in production	23
Good practices in quality control	23
Sanitation and hygiene	10
Self-inspection, quality audits and suppliers' audits and approval	4
Personnel and personal hygiene	9
Equipment	3

Using the approach of chapter 4.4.1 of the main document whereby the main technical challenges were identified as key quality elements for which half or more the assessed manufacturers showed "inadequate" GMP compliance of the key quality elements, the following key quality elements could be identified as main technical challenges using the 2016 assessment results:

- Pharmaceutical Quality System
- Utilities impacting Good Manufacturing Practice (GMP)
- Qualification and validation
- Premises
- Material handling
- Good practices in production
- Good practices in quality control

Table 2 shows a comparison of key quality elements identified as main technical challenges after the baseline assessment and the 2016 assessment.

Table 2: Comparison of key quality elements identified as main technical challenges after the baseline assessment and the 2016 assessment

Key Quality Elements identified as main technical challenges after the initial baseline assessment	Key Quality Elements identified as main technical challenges after the gap assessment in 2016
Pharmaceutical Quality System	Pharmaceutical Quality System
Utilities impacting Good Manufacturing Practice (GMP)	Utilities impacting Good Manufacturing Practice (GMP)
Qualification and validation	Qualification and validation
Premises	Premises
Material handling	Material handling
Good practices in production	Good practices in production
Good practices in quality control	Good practices in quality control

As it can be clearly seen from table 2, the main technical challenges identified during the baseline assessment were identical with those identified after the assessment performed in 2016, verifying adequacy of approach and conclusions made during the Roadmap development regarding the identification of technical main challenges.

As the second part of this comparison, outcomes of the risk categorization of FPP manufacturers made after the 2016 assessment were compared with conclusions drawn from the baseline assessment. The outcomes of the 2016 assessment are presented in table 3.

Table 3: Results of categorization of FPP manufacturers assessed in 2016 based on their compliance with WHO GMP

Risk level Site	Risk level QMS	Overall GMP rating	Number of FPP manufacturers with these ratings	Total number of FPP manufacturers with same "Overall GMP ratings"
1	1	A	0	0
1	2	B	0	2
2	1	B	0	
2	2	B	2	
2	3	C	0	24
3	2	C	16	
3	3	C	8	

The following conclusions can be made based on the results presented in table 3:

- No FPP manufacturer was rated as WHO GMP compliant
- The majority of manufacturers assessed received an overall "C" rating (high risk manufacturer)
- For the majority of manufacturers (16 out of 26 manufacturers) the risk scores for site were higher than the risk scores related to QMS; hence, the main reason for lowering overall GMP compliance were "Site" related GMP aspects

These conclusions made after the 2016 assessment are identical with those made after the initial baseline assessment as outlined in chapter 4.4.2.

Based on the above comparisons of the outcomes of the 2016 assessment and the initial baseline assessment observations, conclusions and prioritizations made based on the baseline assessment for the development of the Ghana GMP Roadmap were confirmed and the adequacy of the GMP Roadmap approach was verified.

2) Technical assistance on CAPA preparation and CAPA review

The technical assistance provided by UNIDO to FPP manufacturers and FDA included besides the gap assessment of 26 manufacturers also CAPA related activities.

As an initial step CAPA training workshops had been conducted by UNIDO for the Ghanaian pharmaceutical industry as well as the FDA. The training workshop focussed on:

- Explanation of requirements and procedures for preparation and review of CAPAs
- Highlighting typical CAPA deficiencies
- Provision of approaches and solutions to overcome typical CAPA deficiencies

After the GMP assessments of Ghanaian FPP manufacturers, it was the responsibility of the manufacturers to prepare their CAPAs for the deficiencies from WHO GMP observed. The CAPAs were reviewed by UNIDO alongside with the FDA. Two rounds of CAPA reviews were performed for each FPP manufacturer whereby the first version was considered a "draft" and the second version was the final version. After review of the "draft" CAPA, each FPP manufacturer was invited to "CAPA clinics". During these CAPA clinics technical advice was provided by UNIDO in conjunction with the FDA to the individual FPP manufacturers assessed in order to assist them in the preparation of adequate and achievable CAPAs. A main focus during these CAPA clinics was on GMP deficiencies for which corrective actions will be time consuming as the manufacturers were required to provide adequate risk mitigations until the corrective and preventive actions had been implemented.

As part of the CAPA clinics further technical assistance was provided to the FPP manufacturers in form of layout reviews for FFP manufacturers constructing new manufacturing sites as part of their CAPAs. Through this activity FPP manufacturers were assisted in the development of GMP compliant layouts for their planned new facilities.

3) Development of the Regional GMP Roadmap Framework for the ECOWAS Pharmaceutical Manufacturing Industry

In the context of the West African Health Organization's (WAHO) ECOWAS Regional Pharmaceutical Plan (ERPP) which describes a comprehensive approach to improving access to essential medicines within the region and targets to reduce the reliance on imported products from outside the region the Regional GMP Roadmap Framework for the ECOWAS Pharmaceutical Manufacturing Industry has been developed. This framework provides a strategic approach within which ECOWAS countries can develop their pharmaceutical industries to adhere to WHO GMP requirements. The GMP Roadmap Framework provides the regional context for the development and implementation of national GMP roadmaps for ECOWAS countries and hence also for the Ghana GMP Roadmap. The GMP Roadmap Framework is an overarching technical reference document for the upgrading of FPP manufacturers to WHO GMP standards.

The framework has been developed after conducting standardized baseline assessments and developing an approach that is relevant across the region. The regional framework supports the risk-based, phased and country specific approach which has been utilized for the development of the Ghana GMP Roadmap and requires that any newly built facilities will have to comply with WHO GMP standards in order to be licensed by the national regulatory authority.

APPENDIX I: KEY QUALITY ELEMENTS AND FOCUS OF COMPANY ASSESSMENTS

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

Note: The terminology of the key quality elements presented in this appendix is based on TRS 961, Annex 3, as at the time of the baseline assessment TRS 986, Annex 2 had not been published.

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

Key quality elements	Subsections	Focus during assessment
1. Quality Assurance 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, investigating and recording • Records • Trending
	Corrective and preventive action	• Applicability of procedure • Responsibilities • System for identification, investigation, corrective and preventive action and follow-up/review • Records
	Change Control	• Applicability of procedure • Responsibilities • System for request, evaluation/classification, implementation, evaluation of effectiveness, close-out • Records, trending
	Regular evaluations of	• Product Quality Review, incl.

	product quality and quality management system	○ 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
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
	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 pipework, 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

	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
4. Qualification and validation	Validation Master Plan	Approach, procedures, responsibilities 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	• Schedules • Calibration frequencies • Elements of qualification (IQ, OQ, PQ) • Protocols • Reports • Ratio of equipment qualified/calibrated to unqualified/not calibrated • Handling of non-qualified, non-calibrated equipment

		• Responsibilities • Standards used and traceability of standards • Tracking/labelling of calibration/qualification status
	Process validation	• Type of process validation in place • Plan • Protocols/reports • Responsibilities • Definition of acceptance criteria • Ratio processes validated to not validated • Handling of non-validated processes
	Analytical method validation	• Plan • Protocols • Reports • Responsibilities • Definition of acceptance criteria • Ratio methods validated to not validated • Handling of non-validated methods
	Cleaning validation	• Plan • 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 of recalls
7. Contract production and analysis	Control of external contract work	• Responsibilities • Evaluation of contractors • Re-evaluation of contractors and frequency • Auditors and qualification • Recording, classification, reporting of observations • Contract/agreements • Records
8. Self-inspections and quality audits	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 / re-evaluation procedure and frequency • Auditors and qualification • Recording, classification, reporting of observations • Follow-ups • Contract/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
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	• Entrance 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 • As point 10

12. Premises	General	• Location • Design/layout and comparison with reality • Material of construction and finishes • Suitability for cleaning and sanitization • Written preventive maintenance and cleaning/sanitation procedures and records • Logical flow of materials, products and personnel • Pest control
	Cleanliness zoning	• Clean zone concept • Separation of areas • Room status labelling •
	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
13. Equipment	General production and QC equipment, 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 • Cleaning procedures, logs • Calibration, qualification procedures, records/logs • Calibration standards • Labelling with calibration, qualification and operational status • Operating procedures/logs • Labelling of fixed pipework • Food grade status of lubricants/coolants in case of product contact
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
	Starting materials	• Material quality • Purchase, storage, handling and control • Procedure defining storage conditions of starting materials • Material codes/ manufacturer internal 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
	Packaging materials (primary or printed packaging material)	• Material quality • Purchase, storage, handling and control • Material codes/manufacturer internal 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
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 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, components, procedures, rooms • Referencing of logbooks/records 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, distribution and version control practices • Handling of electronic data/data

		generated by computerized systems • Traceability • Methods for preparation of working documents from master documents
	Master formulae/Batch processing records	• Design, content, review, authorization, 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 • Reconciliation of labels and printed packaging material
	SOPs and associated records	• System, incl. authorization 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
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 and recording 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
	QC of starting and packaging materials, labels, intermediates, bulk and	• Handling and inspection of incoming materials • Test procedures, defined quality,

	finished products	specifications and records • Availability, use, handling, maintenance, issuance and where appropriate testing and release of reference standards • 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 • Calibration, qualification and validation • Labelling • Cleaning procedures • Traceability of sample history, standards/reagents and quality thereof, equipment, methods, personnel
	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 was uniformly applied to assess Ghanaian pharmaceutical manufacturers in terms of their existing level of compliance with WHO GMP. Each company was assessed for two full working days. The assessment schedule is displayed in table 1.

Table 1: Assessment schedule for the gap analysis of Ghanaian 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
HVAC system
Water system
Compressed air system</td></tr>
</table>

Table 1 (continued): Assessment schedule for the gap analysis of Ghanaian pharmaceutical manufacturers regarding their existing level of compliance to WHO GMP.

<table>
<tr><th colspan="2">Day 2</th></tr>
<tr><td>Morning</td><td>Factory tour (ctd.):

Quality control laboratory

• Wet chemistry laboratory
• Instrumental laboratory
• Microbiology laboratory
• Stability testing
• Retention samples storage
• Laboratory materials management</td></tr>
<tr><td rowspan="2">Afternoon</td><td>Documentation review:
• 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
• Product quality review
• Self-inspections
• Corrective and preventive action (CAPA) procedures
• Rework/Reprocessing procedure
• Review of additional documents</td></tr>
<tr><td>Wrap up and summary of findings /

Closing Meeting</td></tr>
</table>

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 companies 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 is 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

Table 2 (continued): Indicators for score criteria for QMS.

Prerequisite (ctd.)	Rating (continued)		
	1	2	3
Material handling	Documented procedures for all types of material handling are in place in line with pharmacopoeia/ international guidelines	Testing of materials/products is performed but not to the extend required by pharmacopoeia and international guidelines; Procedures for receipt, sampling, storage, manufacturing and distribution are defined but documentation is not in place for all operations	No testing of materials/products is performed; Procedures for receipt, sampling, storage, manufacturing and distribution are inadequate; no GMP documentation is in place
Personnel/ Training	Personnel has the right qualification, experience and knowledge to perform duties assigned, training program is in place	Personnel has the right qualification and knowledge to perform duties assigned, but no training program is in place	Personnel does not have the right qualification, knowledge and experience to perform the duties assigned

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

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