

# SIERRA LEONE GMP ROADMAP

Establishing pharmaceutical manufacturing at internationally recognised GMP standards.

*Produced as part of an ECOWAS regional initiative*







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## LIST OF ABBREVIATIONS

AMRH	African Medicines Regulatory Harmonization
AU	African Union
BOD	Basis Of Design
CAPA	Corrections and Corrective Action Plans
CDA	Compressed Dried Air
ECOWAS	Economic Community of West African States
ERPP	ECOWAS Regional Pharmaceutical Plan
FAT	Factory Acceptance Tests
FDA	Food And Drugs Authority
FPP	Finished Pharmaceutical Product
GAMP	Good Automated Manufacturing Practice
GMP	Good Manufacturing Practice
IQ	Installation Qualification
LPP	Local Pharmaceutical Production
HVAC	Heating, Ventilation and Air Conditioning
NAFDAC	National Agency for Food and Drug Administration and Control
NEPAD	New Partnership for Africa's Development
NRA	National Regulatory Authority
OOS	Out Of Specification
OOT	Out Of Trend
OQ	Operational Qualification
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PMPA	Pharmaceutical Manufacturing Plan for Africa
PMPA-BP	Pharmaceutical Manufacturing Plan for Africa Business Plan
PQ	Performance Qualification
QMS	Quality Management System
RFI	Request For Information
RFP	Request For Proposal
SAT	Site Acceptance Tests
SOP	Standard Operating Procedure

TRIPS	Trade-Related Aspects of Intellectual Property Rights
TRS	Technical Report Series
UNIDO	United Nations Industrial Development Organization
UNAIDS	Joint United Nations Programme on HIV and AIDS
URS	User Requirements Specification
VMP	Validation Master Plan
WAHO	West African Health Organization
WHO	World Health Organization

## 1 INTRODUCTION

This is a national-level technical document. It is designed to outline an approach that allows the establishment of pharmaceutical manufacturers at internationally recognized standards of Good Manufacturing Practice (GMP), specifically WHO GMP. Sierra Leone does not currently have any active pharmaceutical manufacturers, hence the focus is providing guidance on how new facilities could be set up and operated according to these principles.

This document has been developed as part of a regional project which encompasses a move to higher GMP standards for the pharmaceutical industry across ECOWAS. This regional work, known as the ECOWAS Regional GMP Roadmap Framework project, is designed to provide a technical basis for upgrading of pharmaceutical production standards that can be practically applied and presents a pragmatic approach to address the current heterogeneous situation within the pharmaceutical sector across West Africa.

This national roadmap includes an introduction and summary of the Regional Framework project.

It also provides a stepwise approach as a basis for the establishment of new manufacturers in Sierra Leone that are GMP compliant and hence are aligned with the framework that has been validated for the ECOWAS region.

### 1.1 Local production of medicines and the drive to higher quality – health and economic benefits

Healthcare systems within West African countries face significant challenges that negatively impact on access to affordable quality healthcare. Amongst these challenges are the following:

- A high infectious disease burden
- Growing chronic and non-communicable disease burden
- The changing economic context and pharmaceutical industry dynamics
- Shortages in the necessary human resources
- Inadequate distribution infrastructure
- Chronic healthcare underfunding
- Limited access to essential medicines

Against this backdrop, there is a concerted drive across West Africa, and the African continent as a whole, to develop and improve the local manufacturing capacity for essential medicines and vaccines, enabling the increased production of high quality products. In simple terms, this is aimed at delivering the following outcomes:

- Increased access to safe, efficacious and affordable quality-assured medicines

- Establishing a sustainable supply of essential medicines which would reduce dependency on imports to the region which, inter alia, should increase security of supply

And should have the following two overall key impacts:

1. Improved health outcomes
2. Industrial and economic development

## **1.2 The ECOWAS regional initiative to develop the local pharmaceutical sector**

Establishing a strong pharmaceutical manufacturing industry in Africa has been a high profile objective on the continent over the last decade and the Pharmaceutical Manufacturing Plan for Africa (PMPA) as endorsed by the African Union Summit in 2007 explicitly set out the ambition to strengthen this sector to deliver public health and economic development benefits. In solidarity with such an initiative, the West African Health Organization (WAHO) at the 14<sup>th</sup> Ordinary Meeting of the Health Ministers Assembly (Cape Verde, April 2013), signed and adopted the ECOWAS Charter on Public-Private Partnership on Local Pharmaceutical Production of Essential Medicines. This was adopted the same year at the 43<sup>rd</sup> Ordinary Session of the ECOWAS Assembly of Heads of State and Government in Abuja, Nigeria.

This led to the development of the ECOWAS Regional Pharmaceutical Plan (ERPP) 2014-2020 with inputs from ECOWAS Commission, ECOWAS member states and many stakeholders and partners including UNAIDS, UNIDO, WHO and NEPAD. The ERPP highlights one of the key objectives as upgrading manufacturing in the region to achieve internationally recognised standards of production.

Developing the pharmaceutical industry requires coordinated interventions on a number of fronts. ECOWAS and WAHO have made significant advancements for example through establishing the Common External Tariff for pharmaceutical inputs and finished products, making progress on Medicines Regulatory Harmonisation and strengthening quality control laboratories. Progress has also been made on developing policy and guidelines to enable the TRIPS flexibilities to be utilised and measures to address the counterfeit and illicit trade in medicines in the ECOWAS region.

Moving forward ECOWAS and WAHO will look to address additional factors that are critical to enabling companies in the region to upgrade standards and/or maintain them. The GMP roadmap initiative, at the regional and national level, provides the technical framework and technical details regarding the standards. This provides the basis for regional agreement on the timelines that should be established for manufacturers to meet intermediate milestones and ultimately adhere to the internationally recognised standards that will be required as a prerequisite for manufacturing licenses in the ECOWAS region.

## **1.3 Sierra Leone GMP Roadmap – country context**

Sierra Leone has a relatively small population of 7.5 million people. It has a maritime boundary and shares land borders with two countries, Liberia and Guinea. The national medicines regulatory authority is the Pharmacy Board of Sierra Leone.

At present Sierra Leone does not have any pharmaceutical manufacturers and, according to current understanding, there are no specific projects under development that involve the set up of pharmaceutical manufacturers in the country. It is noted that pharmaceutical manufacturing previously took place in the country in the form of a single company. However, it is understood that this ceased operations over twenty years ago. Whilst it may be useful to understand the circumstances leading to the company's closure, the fact that this occurred over two decades ago makes it likely that it will have limited relevance to the present day situation either nationally or regionally.

The majority of legally imported medicines in the country are manufactured in Asian countries, particularly India and China. There are issues in the country relating to substandard and falsified medicines. In common with a number of countries in the region, stakeholders indicate a need to strengthen regulatory capacity in order to improve the level of regulatory surveillance in the marketplace.

One specific issue that is highlighted by stakeholders is the problem of illegal import of medicines. It is noted that the taxes imposed on pharmaceutical products in the country are relatively high when compared to its neighbours (understood to be approximately 25-30% in Sierra Leone versus less than 15% in Liberia and less than 5% in Guinea), and this dynamic is considered to be an added driver to the illegal import of medicines into the country.

It is understood by stakeholders that the relatively small population of Sierra Leone makes it likely that any pharmaceutical manufacturing operation in the country would need to conduct a significant portion of its business in export markets, given that fact that the national market alone is probably insufficient to sustain an economically viable business.

#### **1.4 Purpose of this document**

The Sierra Leone GMP Roadmap is a technical document that 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 including in particular the Pharmacy Board of Sierra Leone, Ministries including the Ministry of Health Sanitation, Ministry of Trade and Industry, as well as other Ministries and other stakeholders.

WHO Good Manufacturing Practice (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. It has been recognised as the required and desirable standard that is to be applied across pharmaceutical manufacturing in West Africa. It is also important to note that many pharmaceutical manufacturers in the ECOWAS region already strive to achieve compliance with WHO GMP, since this forms part of the requirements for having their products prequalified by WHO.

The document is intended to be a reference guide, covering aspects of GMP and related pharmaceutical company development that need to be addressed in order to move towards compliance with both site (facility-related GMP) and QMS (Quality Management Systems) GMP requirements and is consistent with the ECOWAS Regional GMP Roadmap Framework. The

document should be read and utilized in conjunction with the respective WHO GMP guidelines, which are available on the WHO website [www.who.int](http://www.who.int).

### 1.5 Scope of this document

The scope of this document is in line with the ECOWAS Regional Pharmaceutical Plan and the Regional GMP Roadmap framework. The scope includes:

- Manufacturing of finished pharmaceutical products (FPP) for human use which are
  - Medicinal products containing small molecular active ingredients
  - Sterile and non-sterile dosage forms

The scope excludes:

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

## 2 ECOWAS REGIONAL GMP ROADMAP FRAMEWORK

This section provides a brief introduction and overview of the ECOWAS Regional GMP Roadmap Framework. For more information the associated document “A Regional GMP Roadmap Framework For The Pharmaceutical Manufacturing Industry In ECOWAS” can be referred to. The regional framework is relevant to each individual country roadmap given that these national level approaches for development and/or upgrading of the local pharmaceutical sector are all consistent with the regional framework and hence adhere to a common approach. The relationship between the national and regional level initiatives is discussed at the end of this section.

### 2.1 The ECOWAS Regional Roadmap Framework

#### Outline of the framework

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. These are consistent with the overarching parameters established by the framework. Through alignment of all national level roadmaps with a unanimously validated approach, international standards can ultimately be reached across the board. Furthermore, risks during the transition period can be mitigated such that, increasingly, products are quality assured as being safe and efficacious (subject to rigorous product development and approval processes).

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 2018 as regards manufacturers in the ECOWAS region is highly heterogeneous both between countries and within countries. When considering individual member states, Nigeria has well over 100 manufacturers, Ghana has at least 25 active manufacturers whilst others have 4 or less and some do not currently have pharmaceutical manufacturers. Within countries, standards of production vary significantly as has been demonstrated by the baseline assessment process that is described in this document.

It is also important to note that upgrading manufacturing standards is a long-term endeavour and requires not only technical insights and expertise but the combination of many other factors that

create an enabling environment for manufacturers to source investment, technology and human resources amongst other requirements. Manufacturers need support and guidance to develop their businesses and time to implement the upgrading plans that result. In the short to medium term, the risk of dangerous products entering the market from licensed manufacturers can be mitigated through various approaches as described in this document. However, ultimately adherence to GMP is the best way to assure the quality of the products that are produced at each manufacturing site.

### **Baseline assessments of company GMP compliance**

The baseline assessments were conducted across the region in all countries where manufacturing occurs and are summarized in section 3 of this document.

In order to ensure comparability across the assessments the 17 key quality elements that are identified in WHO GMP were broken down into subsections as a basis for conducting the assessments. Similarly a standardized assessment schedule was developed and utilized across all plant visits. Furthermore, observations made during assessments were classified in accordance with pre-defined categories as “critical”, “major” and “other” deficiencies.

Compliance with GMP is a function of physical aspects of the manufacturing plant and organisational issues such as documentation systems and processes; these are summarized respectively as “site” and “quality management systems” (QMS). Based on the observations made during site visits each of the key quality elements was determined as being “adequate”, “needs improvement” or “inadequate”. Consideration of these findings was used to allocate a rating for site and QMS as being low, medium or high risk (1, 2 or 3 respectively) with regard to compliance risk.

In order to derive an overall categorization of GMP compliance a matrix approach was utilised combining the rating for site and QMS. The categorization for manufacturers is A, representing a low risk manufacturer that is largely compliant with WHO GMP; B, representing a medium risk manufacturer that is not compliant with WHO GMP but has reduced risk regarding production safety; C rated manufacturers are high risk, are not in line with WHO GMP and the magnitude of the deficiencies pose a significant risk to production safety.

### **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.

The development of Corrections and Corrective Action plans (CAPAs) is a basis from which companies can upgrade their operations. All companies assessed have been supported to develop such plans. Nigeria is the only country where there are companies that have not been assessed and have not developed CAPAs as part of this process as the size of the industry required that a sampling approach be adopted for this initial stage. The specific means to address this situation are covered in the country's national level roadmap.

CAPA development and implementation are central to risk mitigation; though addressing the most significant issues observed must be a priority at the earliest possible opportunity.

Another area of risk relates to manufacture of product categories and product types. In implementing the roadmap Member States and their development partners could consider utilizing GMP compliance rating at any specific point in time as a basis for determining which products should be reserved for the lower risk manufacturers. However, implementing such an approach requires both highly technical assessments of product categories and individual products as well as rigorous considerations of the possible consequences of such actions.

### **Key features of the framework**

The framework consists of tools and guidance as well as a risk based phased schedule for upgrading standards. It includes the following tools and guidance:

- A tool to assess and categorise the level of compliance of individual manufacturers with each of the 17 key quality elements covered by WHO GMP.
- A tool to categorise (and re-categorise) the overall level of GMP compliance of individual manufacturers as being A (low risk), B (medium risk) and C (high risk).
- 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:

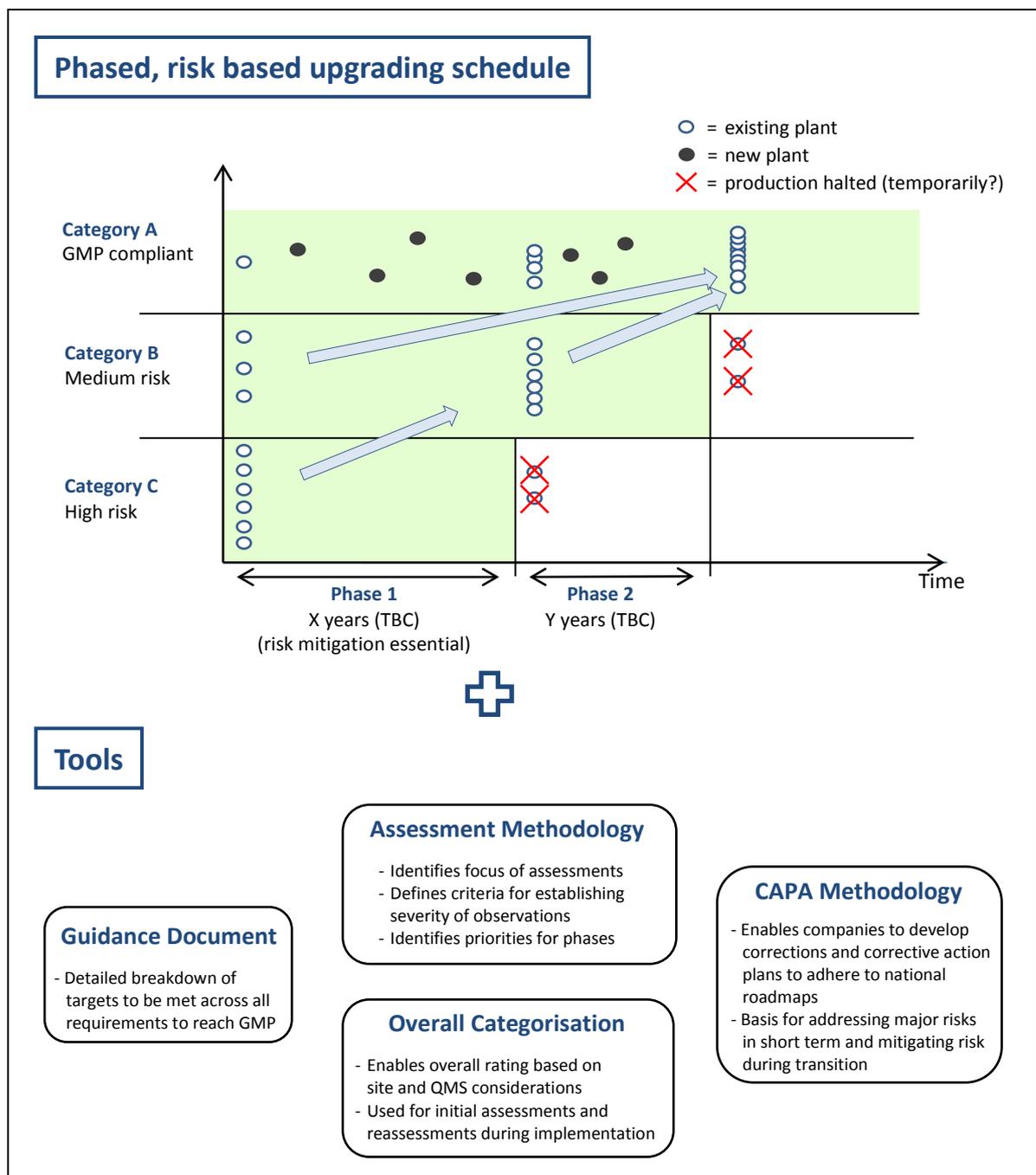
1. A stepwise phased approach to upgrading GMP standards with phase 1 involving all manufacturers reaching at least a B rating and step 2 involving all manufacturers reaching a rating of A, in line with WHO GMP. (The timelines for each phase need to be determined through regional negotiations early on during the 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.

### **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.

**Figure 1: Schematic representation of the key components of the Regional GMP Roadmap Framework**



### **Validation of Framework**

This 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.

## **2.2 Relationship between the ECOWAS Regional Roadmap Framework and the Sierra Leone National Roadmap**

The framework document is an overarching reference document that articulates the regional approach to upgrading of existing and/or implementing new pharmaceutical manufacturing in the region at internationally recognized standards. It establishes a common approach that can then be tailored to the specific situation in each country. Whilst Sierra Leone did not have active pharmaceutical manufacturing at the time of assessments, this national roadmap is consistent with the framework in that one component of the regional document states that any new entrants that establish production facilities in the region should be compliant with internationally recognized standards of production from the start of operations.

Section four of this document provides guidance on how to ensure that new facilities meet these standards before they receive a manufacturing license.

The national roadmaps for other countries in the region where manufacturing is currently taking place includes a section on the methodology that has been used to assess these facilities. This information is included in the Annex to this document.



### 3 FINDINGS

This section describes the findings and key conclusions drawn from the assessments of pharmaceutical manufacturers across ECOWAS member states. It outlines some of the broader regional level findings and also discusses those made at the national level.

#### 3.1 Relevance of regional findings – regional and national level implications

ECOWAS member states fall into one of two categories with respect to pharmaceutical manufacturing, in that they either (a) have active pharmaceutical manufacturing capacity within their country or (b) do not have active pharmaceutical manufacturing capacity.

It is important to recognise the fact that, regardless of the presence or absence of current manufacturing expertise and facilities, every member state within the ECOWAS region benefits from having a stronger regional manufacturing presence that operates in line with international standards of GMP. On this basis, whilst the findings from the company assessment program may not seem to be particularly relevant to a ‘non-manufacturing country’, they are important for a number of reasons:

- The findings from a key part of the regional roadmap design, and impact consequently on national-level initiatives.
- A current ‘non-manufacturing country’ may in time build up a pharmaceutical manufacturing base and the results of the assessments across the region could then be of direct relevance since the typical issues found, and challenges faced, in other ECOWAS member state manufacturers may also be common issues here as well. Therefore, knowledge of the common issues and challenges within the region may help new entrants to focus on particular aspects of their facility design and build, to minimise the risk that they arise here as well.
- Since all ECOWAS member states potentially benefit from increased sourcing of quality assured medicines manufactured from within the region, the current ‘state of the industry’ is of relevance.

#### 3.2 Outline of regional assessment results and evaluation

In total (including the assessments conducted in Ghana) 67 manufacturers of finished pharmaceutical products were jointly visited by local inspectors and UNIDO experts of which 64 were fully assessed in terms of their compliance with internationally recognized GMP standards. The remaining three manufacturers (one each in Ghana, Nigeria and Togo) could not undergo full assessment as they were not operational at the time of the site visit, and therefore had to be excluded from further analysis.

Table 1 shows a breakdown of assessed manufacturers by country. In each of the listed countries but Ghana and Nigeria, all pharmaceutical manufacturers operational at the time have been included in the assessments. In contrast, 11 out of 37 Ghanaian manufacturers have not been visited during early implementation of the national GMP roadmap in accordance with instructions from the FDA, while in Nigeria assessments have been limited to a sample of 25 production sites drawn from a total of more than 180 pharmaceutical manufacturers existing in the country so as to ensure an efficient approach towards framework and roadmap development. The company selection has been conducted in consultation with NAFDAC to ensure representation of different GMP compliance levels, several geopolitical zones, production of various dosage forms (including sterile products) and manufacture of medicinal products considered essential for the Nigerian market.

**Table 1: Breakdown of assessed manufacturers by country.**

Country	Number of manufacturers
Benin	1
Cabo Verde	1
Cote d'Ivoire	4
Guinea	1
Ghana	26*
Mali	2
Nigeria	25**
Senegal	2
Togo	2
* Previously assessed during early implementation of the Ghana GMP Roadmap developed as part of another preceding UNIDO project	
** Sample selection	

The findings show that the majority of companies are currently C rated with a substantial minority categorized as B and a small proportion as A. In more than 50% of the cases, overall site and QMS ratings have been found to differ with the distribution patterns of values for the two criteria showing statistically significant divergence<sup>1</sup>. While the difference for any rating pair does not exceed an absolute value of 1, its median reaches statistical significance<sup>2</sup> with the overall ratings for site outweighing those for QMS. Consequently, where site and QMS ratings are not equal, the overall company classification is far more often adversely determined by site related main technical challenges than by their counterparts associated with QMS. This observation is further substantiated by the finding that the statistically significant rank correlation<sup>3</sup>, which expectedly exists between the respective site and QMS ratings on the one hand and the resulting company classification on the other, shows a far greater magnitude regarding the site<sup>4</sup> than the QMS<sup>5</sup> rating.

<sup>1</sup> Related-samples marginal homogeneity test ( $p < 0.01$ ).

<sup>2</sup> Related-samples sign and Wilcoxon signed rank tests ( $p < 0.01$ ).

<sup>3</sup>  $p < 0.01$

<sup>4</sup> Coefficients

- Kendall's tau\_b: 0.917

While the shortcomings of GMP compliance observed across companies and countries do vary both in degree and the specific key quality elements concerned, a number of regional commonalities have been identified with regard to the main technical challenges to be addressed. These are listed in table 2 below.

**Table 2: Commonalities in main technical challenges observed across the region.**

Observations related to:	
Site	QMS
<ul style="list-style-type: none"> <li>• Premises (e.g. no hygiene zoning, no separation of beta-lactams from other production lines)</li> <li>• Utilities with direct impact on product quality, i.e. relevant inadequacies regarding               <ul style="list-style-type: none"> <li>- Water systems</li> <li>- Air handling systems</li> <li>- Compressed air systems</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Qualification and validation (e.g. no qualification of equipment, no cleaning validation, insufficient [re-]validation of critical equipment)</li> <li>• Production practices (e.g. no environmental control, no hold-times defined and/or validated for the different production steps, no logbooks, incorrect handling of empty drums, insufficient verification of balances, inadequate weighing procedures, incorrect handling of punches and dyes)</li> <li>• Quality control practices (e.g. no stability studies or inadequate stability conditions, no verification or validation methods, insufficient sample retention, no bioburden determinations)</li> </ul>

### 3.3 Sierra Leone assessment results and evaluation

As Sierra Leone currently has no active pharmaceutical manufacturers operating in the country, no assessments were conducted. Therefore, there are no country-specific results and evaluation to report.

It is noted that a pharmaceutical manufacturing facility previously operated in Sierra Leone as mentioned in section 1.3. However as these operations ceased over 20 years ago they are not relevant in the context of the company assessments conducted over the last 24 months as part of the ECOWAS regional pharmaceutical industry upgrading and development program.

- Spearman's rho: 0.935

<sup>5</sup> Coefficients

- Kendall's tau\_b: 0.496
- Spearman's rho: 0.502



## 4 THE SIERRA LEONE NATIONAL ROADMAP

This section describes a strategic approach for the construction of a GMP compliant pharmaceutical manufacturing site. It is informed by the ISPE Good Practice Guide: Project Management for the Pharmaceutical Industry (2011).

### 4.1 Outline of project structure for construction of a GMP compliant pharmaceutical manufacturer

The process of constructing a GMP compliant factory for the manufacture of finished pharmaceutical products can be broken down into three main phases, which can further be broken down into six stages as follows:

**FIRST PHASE:** Project initiation

- **STAGE 1:** Feasibility
- **STAGE 2:** Conceptual development

**SECOND PHASE:** Planning

- **STAGE 3:** Project delivery planning

**THIRD PHASE:** Project delivery

- **STAGE 4:** Design
- **STAGE 5:** Implementation
- **STAGE 6:** Close-out

In practice there is typically some overlap of the phases and stages, especially for the stages 3, 4 and 5.

#### 4.1.1 Phase I: Project Initiation

The project initiation phase can be broken down into two stages:

Stage 1: Establishment of project feasibility

Stage 2: Conceptual development

##### Stage 1: Evaluation of project feasibility

During the project feasibility stage the viability of the project is evaluated. Therefore, after identification of the project, feasibility studies are conducted. Factors evaluated during these studies typically include aspects such as:

- Managerial aspects:
  - Alignment with the company's overall strategy
  - Evaluation of the company's current project delivery capacity → identification of additional resources to be acquired
  - Estimated project duration
- Market analysis:

- Targeted countries for which products are manufactured
- Market needs
- Market pricing scheme
- Market size
- Technical aspects:
  - Availability/adequacy of land/zones for manufacturing
  - Availability of infrastructure
  - Availability/requirements for utilities
  - Availability/requirements for waste management
  - Targeted product classes (e.g. if toxic, sensitizing, mutagenic, beta-lactams, sensitive to light, temperature and/or humidity, sterile/non-sterile, dosage forms) and resulting technical requirements
  - Targeted production capacity (e.g. annual number of tablets, volumes, packs, etc.) and manufacturing environment for targeted product classes
  - Planned operations to be performed at site, including consideration for utilization of non-standard technologies, e.g. melt-extrusion
  - Product development activities to be performed at site (“pure” manufacturing site vs. R&D/scale-up plus manufacturing)
  - Identification of required resources (including materials, equipment, human resources) and their availability
- Regulatory and legal aspects:
  - Required licenses and licensing timelines
  - Regulatory/licensing requirements for countries targeted to be supplied
  - Identification of regulatory/legal bodies to be approached
- Financial aspects:
  - Required investments vs. available financial resources
  - Available financial resources
  - Estimation of running costs
  - Duration for financial returns
- Availability of incentives such as tax exemption or market protection

Taking into consideration the outcomes of the feasibility studies a decision has to be made firstly as to whether, based on the information provided, the project is deemed viable and secondly whether the company is willing to commit to the required resources. In case that the project is deemed viable and the company is willing to commit to the required resources, the project enters the next phase. Otherwise, the project would need to be modified or even possibly postponed or cancelled.

Key aspects of the project are summarized in a “Project charter” which encompasses factors including scope, financial boundary limits, success criteria, main risks, constraints, business benefits, key project team members, and milestones, along with interdependencies to other projects, as applicable. This “Project charter” is typically accompanied by a preliminary project schedule.

## **Stage 2: Conceptual Development**

In the case that the project has been deemed viable, the project conceptual development is performed as the next stage. The purpose of this stage is to identify the most suitable options for

project implementation before further progression of the project to the planning stage. From this stage onwards the project is typically driven by the project manager. Options being evaluated during this stage include:

- Outsourcing approaches vs. in-house operations
- Locations for manufacturing
- Technical/constructional alternatives, e.g. single-floor facilities vs. multi-floor facilities
- Automation concepts
- Most economical flows of personnel and materials/products, samples, waste
- Strategies for separation of GMP areas from non-classified areas
- Separation of maintenance activities from GMP areas
- (Modification of an existing site vs. construction of new site → not applicable in case no prior manufacturing plant existed)
- Alternatives in design
- Requirements for materials of construction
- Simplification of processes
- Equipment replacement strategies in case of equipment failures
- Procurement strategies

The outcomes of these evaluations are summarized in a project delivery strategy which includes an introduction, business case, general project information, organizational chart, roles, responsibilities, project governance, critical issues, procurement and contracting strategy, as well as commissioning and qualification aspects and handover strategy. Preliminary engineering documents may include site plans, conceptual layouts, and high-level process descriptions. In addition, project User Requirements Specifications (URS) are developed and approved as part of this stage and focus on GMP relevant aspects. The URS should be a written description of what should be done (or should happen), but not how it should be done. The URS typically addresses:

- Project scope including product categories, processes, capacities
- Requirements to be met (GMP and legal regulations, standards, business)
- Site requirements (location, constraints, etc.)
- Building requirements
- Documentation requirements
- Commissioning and qualification requirements

The URS is the first stage for qualification related activities. Key aspects for qualification should be defined at this stage in the form of a validation strategy/conceptual validation master plan (VMP). At this stage typically no comprehensive VMP is required but aspects are defined relating to:

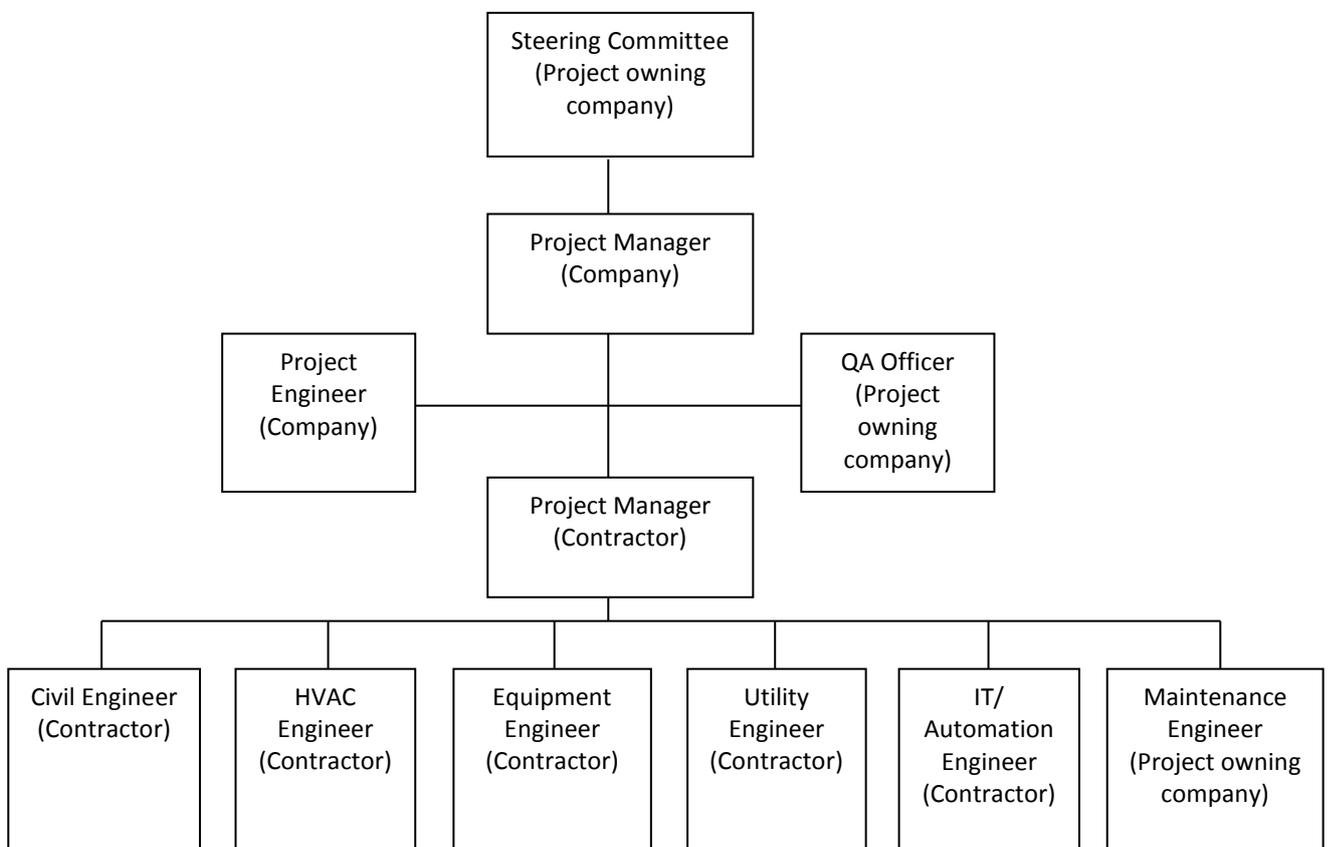
- Overall qualification philosophy

- Life cycles for equipment, utility, automation and building systems showing pre-requisites and interface including the various stages of qualification, documentation and testing requirements
- Requirement and approach for compliant automated systems using, e.g., the Good Automated Manufacturing Practice (GAMP) approach

In order to ensure adequate documentation of all GMP relevant aspects and GMP complaint review of GMP relevant documentation, a quality assurance officer typically forms part of the project team.

The conceptual organogram for a project team could look as follows:

**Figure 2: Conceptual organogram for a project team**



The organogram may be modified throughout the following phases by addition of further subject matter experts as required.

The main task of the QA officer is to ensure that design, documentation, procurement and implementation of design as well as QMS related aspects of the project are in line with GMP requirements.

At the end of this stage a decision will be made by stakeholders as to whether an agreeable option has been identified and whether this option meets business and GMP requirements. The decision as to whether to go ahead to the next project stage or to cancel it should be clearly documented in an updated and signed off project charter.

Typically, after completion of conceptual design a “design freeze” is used to clearly communicate the concepts that are to be built into the future detailed design activities. This also supports change control processes.

#### **4.1.2 Phase II: Planning**

##### **Stage 3: Project Delivery Planning**

After a business case has been developed and approved in stage 2, the focus of the “Project Delivery Planning” phase, after defining the project scope, is mainly on the identification of opportunities and obstacles that may arise during the realization of the project. Detailed planning should be performed to allow for implementation of the concepts defined in phase 2.

As the project evolves, the composition of the project team will be refined, for example, by addition of further subject matter experts as required, and by the definition of communication plans.

A key GMP relevant output of this phase is the development of a validation master plan (VMP). The VMP is a high-level document that establishes an umbrella validation plan for the entire project and summarizes the manufacturer’s overall philosophy and approach. The VMP will be used to establish performance adequacy. It should be clear and concise, and typically contains the following:

- A validation policy
- Organizational structure of qualification/validation activities
- Resources required for qualification/validation
- Risk management principles and approaches
- Training
- Documentation requirements for qualification and validation activities (e.g. procedures, certificates, protocols and reports)
- Qualification of premises, utilities and equipment
- Validation related activities
- Establishing acceptance criteria
- Life-cycle management including retirement policy
- Requalification and revalidation
- Relationship with other quality management elements
- Validation matrix
- References

The VMP may at this stage not address all the above aspects, but will focus mainly on commissioning and qualification related aspects as required for the project.

Another key activity of this phase includes the development of the Basis of Design (BOD) document based on the design option agreed upon in Stage 2. The BOD describes a project’s operating environment and the desired project performance parameters. The BOD transforms the project requirements (the “what”) into a detailed, technical, actionable plan (the “how”) that will meet the

project objectives. The document records the major thought processes behind design decisions made to meet the project requirements. The design team uses the BOD document to show how their approach will enable the completed project to satisfy the requirements defined by the company. This document is developed prior to the issuance of bid specifications and is often used to develop them. The BOD is also called “front end design” and includes descriptions and design schemes covering building, utilities, equipment, zone concepts, flows and other key specifications.

Based on the BOD, URS for the building are developed and/or refined, and URS for key systems and key equipment are developed. The URS typically cover requirements for the following areas and elements: Operational; Functional; Data; Technical; Interface; Performance; Security and Safety; Maintenance; Regulatory Requirements; Life-Cycle; Commissioning and Qualification; Factory/Site Acceptance Tests; Documentation; Organizational.

A project schedule is developed as part of this phase.

At the end of this phase a review is performed to ensure that robust plans are in place. Concomitant with the approval to proceed to the next phase, full funding of the project is typically secured.

At the completion of Stage 3, it is likely that suppliers of utilities, equipment and/or services will need to be engaged to proceed to the detailed design stage.

#### **4.1.3 Phase III: Project Delivery**

The project delivery phase can be broken down into three stages:

Stage 4: Design

Stage 5: Implementation

Stage 6: Close-out

##### **Stage 4: Design**

The main purpose of the design stage is the development of engineering documents to a point of completion which will allow the procurement of utilities, equipment and construction materials. Based on the BOD and the URS developed in Stage 3, detailed engineering documents are prepared.

During the design stage several design reviews are conducted in order to verify throughout the design process that the designs fulfil defined requirements. Design qualification is performed for GMP relevant aspects. Design qualification has to be finalized before construction of GMP relevant aspects of the facility. During design qualification a formal, documented review of design documents and technical specifications is performed in order to ensure completeness and conformity of the design with process, manufacturing, GMP and regulatory requirements. Adequacy of the design is evaluated against the URS.

The design is usually “frozen” at the end of this stage in order to ensure implementation of the agreed and qualified design aspects. Any changes will need to be evaluated through a robust change control.

##### **Stage 5: Implementation**

The implementation stage consists of three main steps:

- procurement

- construction
- testing

The boundaries between these three steps are typically fluid.

The majority of procurement activities commence and/or continue during project implementation. An initial step involves the definition of a procurement strategy. At this stage the URS for GMP relevant items being procured should be finalized. The URS should include clearly stated requirements for factory acceptance tests (FAT), site acceptance tests (SAT), commissioning, qualification and documentation requirements. FAT are tests being performed at the supplier's workshop whereas SAT are tests performed at the user site. FAT are typically required for complex equipment. The next step is short listing or pre-qualification of suppliers. During this pre-qualification process a "Request for Information (RFI)" is sent to suppliers in order to evaluate their skills, capability, experience with specific project related aspects, cost estimates, financial viability of the supplier and the supplier's GMP understanding for the services requested. Out of the short-listed suppliers, typically two or three in number, a supplier is selected based on its capability to implement the technical requirements. For this selection process a "Request for Proposal (RFP)" is sent to the pre-qualified suppliers. The RFP typically contains budgetary considerations and a confidentiality agreement in addition to technical requirements such as URS, specifications and drawings. Based on the suppliers' bids, the supplier that has demonstrated best compliance to the requirements defined in the RFP is selected and contracted.

Design qualification related aspects need to be finalized before construction of the respective factory/utility/equipment/item or, for off-the-shelf equipment, before acquisition of the equipment.

At the end of the procurement step a check should be made to ensure that all required items and/or equipment have indeed been procured.

During the construction phase of the facility it is necessary to ensure that that the construction complies with the previously defined requirements. Therefore it is important to start with testing and documentation aspects, such as commissioning activities, at an early stage of the construction process in order to ensure construction quality, i.e. compliance of the construction with the predefined requirements. In practice it will be, for example, quite difficult to verify compliance of piping with the defined specifications after finalization of their installation which may even include insulation. "Commissioning", in the context of new facility design and development is typically considered to involve a well-planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the end-user. This would result in a safe and functional environment that meets established design requirements and stakeholder expectations. Commissioning is a comprehensive check that aspects of the design have been met and in order to verify installation and operational functionality. Commissioning can be understood as a pre-cursor to qualification activities, in contrast to commissioning qualification activities which typically focus on GMP aspects that have been identified as having a direct impact on product quality, using the risk assessment strategy defined in the VMP.

The next qualification step is installation qualification (IQ). This involves the documented verification that the facilities, systems and equipment, as installed, comply with the approved design and approved specifications. During IQ it is also necessary to ensure that all required documentation has been received from the supplier. This may include materials such as operating and working

instructions and manuals and maintenance, cleaning and calibration requirements which will form the basis for the development of related SOPs. Further documents include drawings, piping & instrumentation diagrams, print outs, certificates and software documentation.

After mechanical completion of constructions and installations, finalization of SAT/commissioning and IQ, operational qualification (OQ) is performed. OQ is the documented verification that the facilities, systems and equipment perform as intended throughout the anticipated operating ranges. During OQ, operational parameters that have been identified as critical are tested and challenged against defined specifications. Another key activity during OQ is the finalization and approval of SOPs, typically those relating to operation, cleaning/sanitization, calibration and maintenance. This also includes the provision of SOPs relating to the training of operators for the systems and equipment, and for the maintenance of training records. After the finalization of OQ, the factory is ready for handover to the project owning company.

Performance qualification (PQ) related activities constitute the documented verification that the facilities, systems and equipment, as connected together, can perform effectively and reproducibly, based on the approved process method and product specification. These activities are frequently performed by the project owning company after handover.

#### **Stage 6: Close out**

The close-out activities include the following:

- Handover activities, which include knowledge transfer from the project team to the project owning company and the handover of all project drawings and documents to the project owning company. The handover may also include hiring of staff, identification of work locations and training of company staff
- Financial and contractual close-out, which includes clearance of all invoices with the financial department as well as the management of warranties and guarantees
- Contractor/vendor performance evaluation
- Project data base close out, including actual completion data and actual hours spent versus initially planned
- Stakeholder satisfaction survey and lessons learned discussion. This includes a meeting between the Project Team and stakeholders to discuss lessons learned and project satisfaction. The Project Team should document the feedback from this discussion. The feedback should be used by the Project Team and the relevant organization to improve future project management performance

A successful project will result in the design, construction and qualification of a GMP compliant pharmaceutical manufacturing site. However, not all GMP aspects related to the quality management system (QMS) would yet be in place. It is the task of the project owning company to identify aspects of the QMS which are not yet developed and implemented, and establish a comprehensive QMS. It is therefore necessary to ensure that, besides a GMP compliant site, a comprehensive GMP compliant QMS is also in place before licensing of the new pharmaceutical factory.

## 5 ENABLING ESTABLISHMENT OF NEW, GMP COMPLIANT PHARMACEUTICAL MANUFACTURING FACILITIES: OTHER STRATEGIC CONSIDERATIONS

The Sierra Leone Roadmap provides guidance on how to ensure that new manufacturing facilities meet internationally recognized standards from the start of operations. This guidance is technical in nature and should be of particular relevance to the Pharmacy Board. However, establishing internationally recognized manufacturing facilities in the country is likely to require decisions and involvement of a number of different national stakeholders given the range of factors that need to be addressed to create a conducive environment. These include, but are not limited to, policymakers and other Government-related bodies as well as additional public and private national-level organisations. In particular, the Ministry of Health and Sanitation, and Ministry of Trade and Industry are likely to play key roles.

To realise the objective of building, commissioning and operating new facilities in compliance with internationally recognized GMP that will be commercially viable, there are various other strategic issues that need to be addressed in parallel with roadmap implementation. As this document focuses on technical matters, it is not appropriate to cover them in depth or prescribe specific solutions but some of the most common other components are summarized below. The process of identifying the exact specific components that need to be addressed in an individual country, determining an appropriate strategy, and executing this, rely on the involvement and decision-making of the relevant national entities. As such, the following section serves to highlight a number of components that are likely to be relevant. The components summarised below do not therefore represent a comprehensive and complete list but are highlighted since they are likely to be of relevance, to a greater or lesser degree. The identification and definition of a complete set of strategic components can be addressed during follow up and implementation.

### 5.1 Strategic components likely to be required for national level roadmap implementation

Typically, a holistic strategy is required in order to establish an environment that supports pharmaceutical industry upgrading. It is likely that the following elements will need to be addressed – to a greater or lesser degree – to ensure that companies can successfully achieve and maintain international standards of drug manufacture.

- **Access to finance.** Existing companies requiring upgrading, and new entities, typically require finance in order to invest in improved manufacturing facilities and QMS systems or set these up in the first place. The degree of investment capital required varies from company to company and depends on a number of factors including the state of current manufacturing operations, the size of the company, and whether the upgrading process involves a degree of expansion as well. Most manufacturers, apart from those already operating at high standards, will require a source of external capital in order to conduct facility improvements, or establish their new facility, in an acceptable timeframe. This timeframe needs to take into

account both commercial and regulatory considerations. Access to affordable capital is therefore an important component for most pharmaceutical industry upgrading programs. Foreign direct investment (FDI), whereby a foreign entity – in this case an individual or more likely a company already involved in pharmaceutical production – invests in a project to develop a new manufacturer in a separate country, is also a good potential course of capital in the case of such ‘green field projects’, and could play a key role in the situation where a new pharmaceutical facility is being set up.

- **Regulatory strengthening.** The National Regulatory Authority needs to be suitably staffed, resourced and equipped to monitor and enforce medicines production at high standards. This is important to ensure that medicines manufactured with the country, and those imported, meet the necessary quality requirements. Typically, in order to develop a fully functioning NRA, a degree of regulatory strengthening is required. This is likely to involve support, and potentially training, from suitably qualified and experienced international agencies. An initial step may require analysis of areas where improvement is required and this can then be utilized to create an implementable development plan for the NRA.
- **Governance.** Development of a pharmaceutical sector – whether this involves many or few companies - requires concerted action of a number of stakeholders over a multi-year time period. In order to ensure that industry development is properly planned and executed, these stakeholders need to work together in a coordinated fashion to ensure that appropriate actionable and achievable plans are developed, implemented and monitored. To do this, an appropriate Governance structure needs to be set up. This structure should contain the appropriate entities (i.e. stakeholders) and be formed in such a way that the governance mechanism itself is one that functions effectively. It may involve two or more tiers, whereby there is a working level committee or body that ensures implementation of the roadmap and works to address challenges faced at a practical level. This may need to be complemented by a strategically-focused higher level body that forms the interface between Government and the working level group.
- **Incentives.** It is generally understood that in order to both encourage and support pharmaceutical manufacturers transitioning towards higher production quality standards, incentives are required. These may be financial or non-financial in nature. Typically, a suitable package is designed with involvement of the appropriate Ministries (including Health, Industry and Finance), the National Regulatory Authority, and industry itself. The incentives are likely to be provided on a time-limited basis – usually including the length of the roadmap itself – and serve to provide a ‘level playing field’ such that companies that have already invested in higher quality and that incur a higher cost of goods, can compete against those still at lower quality and with a lower cost base during the transition period before all companies within the market are operating at a higher quality standard.
- **Human resource.** A pharmaceutical industry cannot be upgraded without a parallel upgrading of human resources in the sector. This initiative could be implemented on two fronts: increasing the absolute output of personnel with the necessary skills and training to support an expanded and growing pharmaceutical sector; and continuing skills and know-how development to build capacity within the pharmaceutical companies on an ongoing basis. The personnel required by the industry includes pharmacists, in particular industrial

pharmacists, as well as engineers, chemists, microbiologists and biochemists, technicians, and other professionals. Depending on the potential overall growth in the industry, it may be necessary to work with local universities and other training institutions so the output of trained individuals emerging from these establishments meets industry needs. Training courses and programmes, including basic GMP, could therefore involve both current and potential future employees. It is also necessary to examine HR requirements within the National Regulator and develop suitable training opportunities for both existing staff and again students that may take up new positions created within the NRA. The development of a skilled work force will take time. However, in the short term there is a need for companies to access know-how and to design programmes to meet the requirements of the GMP roadmap. On this basis, it is not unusual to import personnel with the required skill set and experience in the near term if this is financially viable (in the case that suitably qualified and experienced individuals are not found in the country already).

- **Political will.** The establishment and maintenance of ongoing and demonstrable political will is a key component that facilitates and supports a successful industry upgrading process. It is necessary to set up an enabling environment which both drives and encourages companies, both new and existing, to take the necessary steps to manufacture medicines at high quality standards. As the process is undertaken over multiple years, sustained political will is a requirement. It also serves to encourage other key entities to become involved. This includes, in particular, both national level and international investors, who generally make their investment decisions having taken a view on the overall enabling environment that exists within the particular sector.

## 5.2 Proposed comprehensive program for development of regional pharmaceutical industry

This roadmap is a country level technical document and is intended to be operationalised in line with the regional framework and in the context of pharmaceutical industry development being a regional priority for ECOWAS, with the required commitment over an extended period of time. This means that there needs to be appropriate coordination and agreement between the regional level programme and its respective member states. There are, in particular, various strategic and operational considerations that need to be taken into account when looking at the regional perspective, and given the fact that implementation of the actual upgrading process takes place by and large at a national level. It is, therefore, likely to be of benefit to individual member states' pharmaceutical development initiatives if they are structured and coordinated in such a way as to benefit from the relevant regional level activities and programs. The following are examples of such factors that need to be taken up.

- There should be consideration of the degree to which ECOWAS member states can move towards a single market for pharmaceutical products, since, inter alia, attracting investment and technology, and operating efficiently will require that ultimately, manufacturers have access to a substantial market.

- It will also be necessary to consider how the ranges and types of incentives can be fairly defined whilst considering the situation across the region, such that the pharmaceutical sector in one particular country does not overly benefit, at the expense of its neighbour. It is also important to ensure that, as a whole, West African manufacturers are enabled to invest and compete with imported products. Such issues will be complicated by the existence of multiple currencies within the region, where depreciation and interest rates may fluctuate over time (though the impact will be reduced as and when a common ECOWAS currency is introduced).
- Whilst there is an on-going process for regulatory harmonisation and a common external tariff in place, there remain significant non-tariff barriers to intraregional trade in pharmaceuticals. The degree to which these can be limited may also have direct bearing on the timelines for implementation of the stages of the framework. Ultimately the timelines may be country specific or determined at the regional level.
- During the development of the regional framework and the national level roadmaps the level of GMP compliance for assessed companies has been kept highly confidential. Once all manufacturers have been assessed and as companies develop, there may be value in making such categorisations available to specific entities or more broadly. This is a highly complex and sensitive topic but needs to be resolved as part of the implementation approach. Central to the roadmap approach are the development of CAPAs and the re-categorisation of companies. A robust, transparent and efficient mechanism for monitoring CAPA implementation and for re-categorisation of companies will need to be developed. For Sierra Leone and other countries that may be developing new industries as well as the new manufacturers, the reassurance of a transparent regional development process and enforcement across ECOWAS is likely to be important in securing investment.

## 6 CONCLUSIONS

The Sierra Leone GMP Roadmap is a national level technical document. It outlines an approach to the establishment of pharmaceutical manufacturing operations in the country that have the capability to produce medicines at WHO GMP, which is a widely recognised international quality standard.

The document has been developed as part of a collaboration between WAHO and UNIDO to establish an overarching Regional GMP Roadmap Framework and national level roadmaps that are aligned to the key principles and components therein. The regional framework establishes a common approach addressing technical issues that, to a greater or lesser extent, have been identified through assessment of current manufacturing in the region. It also sets common milestones towards ultimately ensuring that all manufacturing in West Africa is effectively compliant with internationally recognized GMP. An outline of this overarching technical approach is provided in this document.

Although Sierra Leone currently does not have pharmaceutical manufacturing facilities, the Sierra Leone GMP Roadmap defines an approach to develop production sites compliant with internationally recognised GMP standards. This involves a multi stage process that includes clear project initiation, planning and delivery stages. By adopting such an approach, stakeholders including Government entities, the national medicines regulatory authority and the project backers themselves can work together to deliver a well set up, high quality facility with the correct quality management systems in place. It is worth noting that pharmaceutical manufacturing operations previously existed in Sierra Leone, so there is a history in the sector within the country although this facility has not been active for a large number of years.

Development of a functioning, commercially sustainable pharmaceutical sector involves ongoing interactions and efficient communications between key parties including, in particular, the Ministry of Health and Sanitation, Ministry of Trade and Industry, the Pharmacy Board of Sierra Leone and companies themselves. To allow effective coordination of these entities and other relevant stakeholders, it is beneficial to set up a working group and/or committee in the event that the country moves towards development of a pharmaceutical sector. This structure is designed to ensure timely discussion and agreement on key steps and other aspects related to the planning, execution and regulatory oversight when new pharmaceutical production facilities are being established.

As well as the technical dimensions of such an undertaking, there are a number of other components that are typically involved. These include, but are not limited to, aspects such as access to finance for the construction of new facilities, provision of suitable incentives to support the establishment of the industry, human resource and skills development to ensure availability of an adequately trained and experienced work force and, potentially, regulatory strengthening. In addition to these components, continuing political will and support is likely to be a key driver for the successful development of the sector.

It is important to note that there is no assumption that Sierra Leone will, or should, develop a pharmaceutical industry. The move to establish, or facilitate the establishment of, pharmaceutical manufacturing is a country level decision involving the relevant stakeholders within Sierra Leone. Therefore, this Sierra Leone GMP Roadmap document provides technical guidance regarding the establishment of new pharmaceutical manufacturing facilities that are compliant with international

standards and hence also consistent with the regional framework, should the country decide to move in this direction.

Regardless of the country-level decision whether or not to develop pharmaceutical manufacturing in Sierra Leone, the objective of strengthening the regional pharmaceutical industry should contribute to improved access to safe, effective and affordable essential medicines for citizens of all ECOWAS Member States. A strengthened pharmaceutical manufacturing industry in West Africa that complies with internationally recognized standards of GMP will reduce reliance on medicines imported from further afield. In this way all West African states should benefit from, inter alia, improved security of supply and increased regulatory oversight for products entering the market given logistical and resource realities, when the national regulatory authorities are situated in relatively close proximity to the manufacturers themselves.

Implementation of the Regional Framework and the national level initiatives (in countries seeking to initiate or promote growth of their pharmaceutical sector) require many issues (over and above the technical aspects that are the focus of these documents) to be addressed to enable companies to make investments, access technology, access skilled human resources, compete in a defragmented regional market where quality of production is a prerequisite, supply international procurement entities and receive appropriate time limited support in developing their businesses.

This is a multi-year undertaking and, as is discussed in this document, it is intended that a comprehensive programme be established to support national initiatives and the regional structures and agreements that will be required to be sustained over an extended period of time. The objective of establishing this comprehensive programme has been agreed between WHO and UNIDO. On 27 May 2019 the Directors General of the two organizations signed a Relationship Agreement establishing a legal basis for a long term collaboration to support the implementation of the Regional GMP Roadmap Framework and to support overall strengthening of the pharmaceutical industry in West Africa.

## ANNEX: APPROACH AND METHODOLOGY OF COMPANY GMP ASSESSMENTS

This Annex describes the approach used to assess pharmaceutical manufacturers in ECOWAS member states as part of the development of the Regional Roadmap Framework. The approach takes account of the WHO GMP quality standards and utilises two related tools that have been specifically designed to allow determination of the operational deficiencies (including both site and QMS related deficiencies) that exist in a pharmaceutical manufacturer. By doing this, it is possible to analyse the variance between a manufacturer's current GMP standards compared to WHO GMP requirements and provide an overall GMP classification for the company. This is a key component in both the roadmap itself and the individual company upgrading program that is executed in order to move towards WHO GMP compliance, for a manufacturer that is currently operating.

This Annex should be considered in parallel with the related framework-level document "A Regional GMP Roadmap Framework For The Pharmaceutical Manufacturing Industry In ECOWAS" (2019) and, in particular, the Annex and Appendices attached to this document:

- The Annex consists of a guidance tool providing information summarising the technical requirements of each of the 17 Key Quality Elements that comprise WHO GMP
- The three Appendices contain further information relating to the assessment and grading process and are therefore of relevance when understanding how the assessments are conducted and how this process leads to a company's GMP classification

### Approach

#### GMP reference standard for company assessments

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

#### Key quality elements

The assessments were based on the 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 has been divided into sub-sections for which the assessment focus was defined. Through this approach, 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 of the document “A Regional GMP Roadmap Framework For The Pharmaceutical Manufacturing Industry In ECOWAS”.

Based on the defined key quality elements and the areas of focus, an assessment schedule was prepared which has been uniformly applied to all pharmaceutical manufacturers involved. Each manufacturer was assessed over two full days. The assessment schedule is displayed in Appendix II of the document “A Regional GMP Roadmap Framework For The Pharmaceutical Manufacturing Industry In ECOWAS”.

#### **Rating of observations: critical, major and other deficiencies**

Observed deficiencies were rated based on the compilation of EU community procedures on inspections and exchange of information (London, 3 October 2014, EMA/572454/2014 Rev 17) and adapted for the assessment process:

##### Critical Deficiency:

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

##### Major Deficiency:

A non-critical deficiency,

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

*or*

which indicates a major deviation from Good Manufacturing Practice;

*or*

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

*or*

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

*or*

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

#### Other Deficiency:

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

### Scope

The scope of the regional framework is in line with the ECOWAS Regional Pharmaceutical Plan. The scope includes:

- Manufacturers of finished pharmaceutical products (FPP) for human use which manufacture
  - Medicinal products containing small molecular active ingredients
  - Sterile and non-sterile dosage forms

The scope excludes:

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

### Tools used to assess the pharmaceutical manufacturers

In order to evaluate the level of compliance of pharmaceutical manufacturers with WHO GMP, and to identify the main technical challenges across the range of FPP manufacturers to establish a baseline, two tools were developed to ensure standardization of the findings:

**Tool 1:** Categorisation of compliance with each of the 17 key quality elements

**Tool 2:** Categorization of a FPP manufacturer’s overall compliance with WHO GMP

#### **Tool 1: Categorisation of compliance with each of the 17 key quality elements**

This tool provides a measure of the compliance of the company to each of the key quality elements. Using the plain ratings of individual observations made during each assessment is not suitable due to the variety of individual observations. Therefore, based on the rating of observations made during the GMP assessments, the compliance to each key quality element was determined using a rating key. This made it possible that observations related to a specific key quality element could be rated as a whole based on the combination of specific observations and thereby reflect the overall compliance of the respective key quality element with WHO GMP requirements. Key quality elements were rated using the following key:

- **Acceptable:** Compliance of a key quality element with WHO GMP was rated “acceptable” if no or only “other” (i.e. “minor”) deficiencies were observed in areas related to this specific key quality element.
- **Improve:** Compliance of a key quality element with WHO GMP was rated “requires improvement” (short: “improve”) if only a few ( $\leq 5$ ) “major” deficiencies were observed in areas related to this specific key quality element.
- **Inadequate:** Compliance of a key quality element with WHO GMP shall be 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 is not available at a manufacturer.

This rating key fulfilled the requirement to rate the performance of FPP manufacturers regarding WHO GMP compliance for each key quality element.

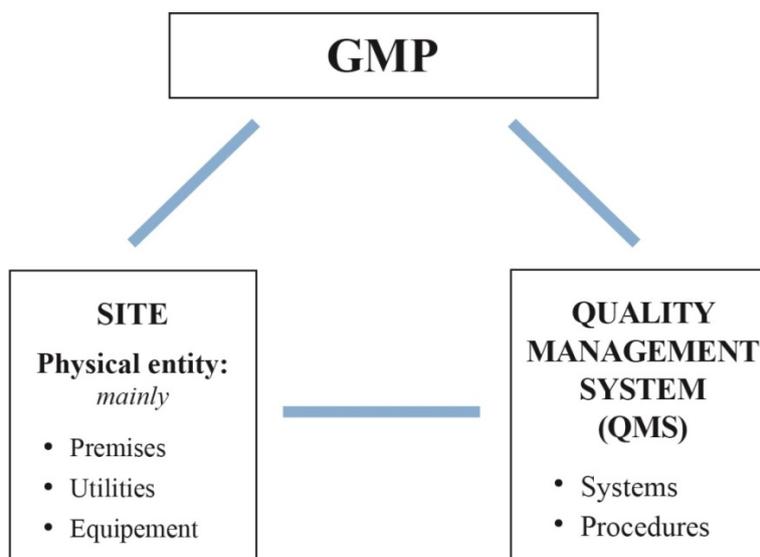
Furthermore, the described rating tool allows for prioritization and streamlining of CAPA activities at manufacturer level by identifying key quality elements having the highest impact on the manufacturer’s compliance with WHO GMP.

#### **Tool 2: Categorization of a FPP manufacturer’s overall 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 can vary significantly between pharmaceutical manufacturers. The spectrum can range from FPP manufacturers that are compliant with WHO GMP requirements to those that have multiple critical issues to address.

The probability that a significant range in level of adherence to GMP compliance by pharmaceutical manufacturers exists across the region required the use of a tool for categorization of the compliance risk associated to the pharmaceutical manufacturers under assessment.

Each manufacturer assessed was categorized according to its level of compliance with WHO GMP. This categorization is based on the understanding that GMP compliance is a result of 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 manufacturer to ensure GMP compliance. The interconnection between site, QMS and GMP is illustrated in figure 3.

**Figure 3: Interconnection between Site, QMS and GMP**

This rating tool uses a matrix to categorize pharmaceutical manufacturers based on the two risk-indicating factors for GMP compliance:

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

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).

A level of “1”, “2” or “3” was assigned to both site and quality management systems to describe their compliance with WHO GMP, with a level of “3” representing a high compliance risk, and a level of “1” representing a low compliance risk.

A matrix, shown in figure 4 below, was used to combine these two levels in order to generate an estimate of the compliance risk associated with a pharmaceutical manufacturer. The resulting risk ratings are “A”, “B” and “C”. A rating of “C” indicates high risk manufacturers with non-compliance to WHO GMP, even causing a high risk to product/production safety. A rating of “A” indicates low-risk manufacturers, where the existing approach towards pharmaceutical manufacturing is, in general, in line with WHO GMP requirements.

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

the document “A Regional GMP Roadmap Framework For The Pharmaceutical Manufacturing Industry In ECOWAS”.

**Figure 4: 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

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

This risk categorization was used to establish the level of GMP compliance of all manufacturers assessed. It can also be used to monitor the manufacturers' development towards full WHO GMP compliance over time. The tool enables identification as to whether main technical challenges faced by the FPP manufacturer are related to site or quality management system in case differences in the risk levels for "site" and "QMS" are observed. As this tool allows the identification of main technical challenges and the risk associated to manufacturing activities by individual manufacturers, the tool also allows for prioritization and streamlining of CAPA activities. Therefore, the categorization of FPP manufacturers according to their WHO GMP compliance is a key tool of the regional framework.







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