A REGIONAL GMP ROADMAP FRAMEWORK FOR THE PHARMACEUTICAL MANUFACTURING INDUSTRY IN ECOWAS

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2019

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This document has been prepared under the overall guidance of Alastair West (UNIDO's Business Plan Coordinator - Pharmaceutical Manufacturing Plan for Africa), with Kay Weyer (Lead GMP Expert) being the other principle author. Significant contributions have been made by Martin Nicholson (Pharmaceutical Sector Expert), Wilko von Klüchtzner (Associate Industrial Development Expert), Assane Coulibaly (Regional Project Coordinator, West Africa) and Uche Sonny-Afoekelu (National Expert, Nigeria). Technical inputs have been provided by Alain Kupferman, Arie Maat, Sue Mann, Nathalie Valle and Ibelema Emeh.

This document has been prepared in close cooperation with the West African Health Organization (WAHO), represented by Carlos Brito and Sybil Ossei Agyeman Yeboah. There has been strong collaboration with national regulatory authorities across the region, particularly the National Focal Points for each country as nominated by their respective Ministers of Health. The private sector has also played a key role throughout the process, with involvement including a number of national Trade Associations. Particular gratitude is due to the West African Pharmaceutical Manufacturers Association and its President Okey Akpa.

The document forms part of an ongoing collaboration between WAHO and the United Nations Industrial Development Organization (UNIDO) to develop a strategy for region-wide upgrading of the pharmaceutical industry across West Africa. Subsequent expected steps of the program will include development and execution of implementation plans at both regional and national levels, covering the development of the pharmaceutical industry towards WHO standards of Good Manufacturing Practice (GMP). The current phase of the program is funded by WAHO.

FOREWORD

Increasing access to high quality, affordable essential medicines is a fundamental requirement to enable the Economic Community of West African States (ECOWAS) and its Member States improve public health of our citizens. At present our region relies on imports for over 80% of our essential medicines. This situation leaves us vulnerable to supply constraints and makes effective regulation of suppliers of the majority of our medicines a huge challenge for the Medicines Regulators in the region. It has further consequences such as limiting our ability to respond to regional health emergencies and leaves us dependent on imports for products funded by international donors, particularly for treatment of HIV/AIDS, malaria and tuberculosis.

The West African Health Organisation (WAHO) is the Specialised Institution of ECOWAS that is responsible for ensuring the attainment of the highest possible standard and protection of health of the peoples in the region through the harmonization of the policies of the Member States, pooling of resources, and cooperation with one another. As part of initiatives to deliver on this mandate, WAHO developed the ECOWAS Regional Pharmaceutical Plan (ERPP) in 2014. This plan includes a number of different components and a central one is to reduce our reliance on imports through the development of the pharmaceutical manufacturing industry in the region.

As is detailed in the ERPP, developing the pharmaceutical sector is a multifaceted undertaking that requires long term support to the industry and associated stakeholders such that internationally recognised Good Manufacturing Practices (GMP) can be achieved and sustained. This support is required at the national and regional levels and it is imperative that risks relating to the safety and efficacy of products are minimised during the transition process.

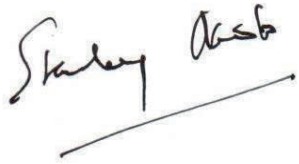
This document has been prepared following a rigorous diagnostic process to ascertain the current status of the industry across the region and the variation in quality standards that are currently in place. Importantly, it sets out a framework utilising a risk-based phased approach for the upgrading of manufacturing sites that can be adapted for specific country contexts. In so doing it establishes common principles to enable Member States to develop their pharmaceutical manufacturing sectors such that we can move towards an increasingly defragmented pharmaceutical market in the region. This will benefit all Member States through improving access to high quality essential medicines that can be produced more affordably if manufacturers are serving a regional market of over 350 million people rather than smaller national level markets.

Developing the pharmaceutical industry in the ECOWAS region is a long term undertaking that will require many issues to be addressed and commitment from key stakeholders. As we move forward with the process, substantial benefits will be realised. For example, we can quickly mitigate against critical problems that can inadvertently lead to substandard products being released into our market. Leading manufacturers can more rapidly achieve the international standards required to supply the international donor markets. We can expand the range of products manufactured within the region not least through technology transfer, and we can attract investment that, over and above the health benefits associated with improved access to quality assured medicines, will also contribute to economic development of the region.

It is recognised that development of the pharmaceutical industry to enable us to become more self-reliant in terms of essential medicines production is a challenging undertaking. However, it is eminently

achievable and this framework represents a central component of the process. Furthermore, the framework is a tool to guide and support the industry, and to monitor its development in a transparent way, ensuring that we have regional unity with regard to the industry upgrading process.

WAHO remains committed to reducing the reliance of the ECOWAS region on imports, and to improving access to high quality affordable essential medicines. This framework provides the technical basis and guidance for upgrading the pharmaceutical manufacturing sector, thereby enhancing achievement of the region's public health and broader development objectives.



Professor Stanley Okolo

Director General

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LIST OF ABBREVIATIONS

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

* In this document the term CAPA is used with a focus on corrections and corrective actions

EXECUTIVE SUMMARY

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".*

Why is a framework necessary?

This document is a corner stone of this strategic approach as it provides a framework within which countries can develop their pharmaceutical industries to adhere to international Good Manufacturing Practices (GMP). Complying with this standard (as well as being subject to rigorous product development and approval processes) ensures that the quality of medicinal products is assured consistently and that they are 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 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.

This is a technical reference document that provides guidance and requirements for pharmaceutical manufacturers within the region to upgrade their facilities. This is an overarching framework for the region which has been adapted to the specific national contexts in the form of national GMP roadmaps, and supports companies at different stages of their development to progress towards compliance with international GMP standards.

To develop this framework a robust methodology was utilized that included determining the reference GMP standard, defining the scope of the framework, conducting standardized baseline assessments and developing an approach that is relevant across the region.

WHO GMP as the reference standard

WHO GMP has been identified as the reference for this framework for a number of reasons including:

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

Using this reference as a basis, the framework has been developed for sterile and non-sterile products for human use but excludes products that involve complex biological molecules.

Baseline assessments of manufacturer GMP compliance

The baseline assessments were conducted across the region in all countries where manufacturing occurs. 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 the 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 companies 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, representing a high risk manufacturer, which is not in line with WHO GMP and where the magnitude of the deficiencies poses a significant risk to production safety.

A total of 64 companies have been included in the baseline assessments, comprising 26 manufacturers assessed and graded in Ghana as part of another UNIDO project and 38 companies assessed and graded specifically as part of this ECOWAS GMP Roadmap Framework project. In Nigeria a methodology was developed to identify a representative sample of 25 companies across geopolitical zones, perceived GMP status and product forms produced. All other manufacturers operating in the region were assessed. The findings show that the majority of companies are currently C rated with a significant minority rated as B and a small proportion as A.

Insights from assessments for design of framework

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

- Provide a consistent methodology for categorization of the level of GMP compliance.

- Provide 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.

- Utilize 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).

- Include agreement that all new manufacturers should be GMP compliant prior to receiving a manufacturing license.

- Include measures to mitigate risk during the transition to WHO GMP compliance.

Furthermore the framework recognises that not all companies start at the same point and that for the more advanced companies guidance on achieving international standards in the short term would be beneficial as it could enable/expedite their ability to access international donor funded markets. Hence, for all companies (and for regulators) the detailed guidance in the Annex is a critical source of information.

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. The specific means to address this situation are covered in the 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 point in time as a basis for determining which products should be reserved for the lower risk companies. However, implementing such an approach requires both highly technical assessments of product categories and individual products as well rigorous considerations of the possible consequences of such actions.

Key features of the framework

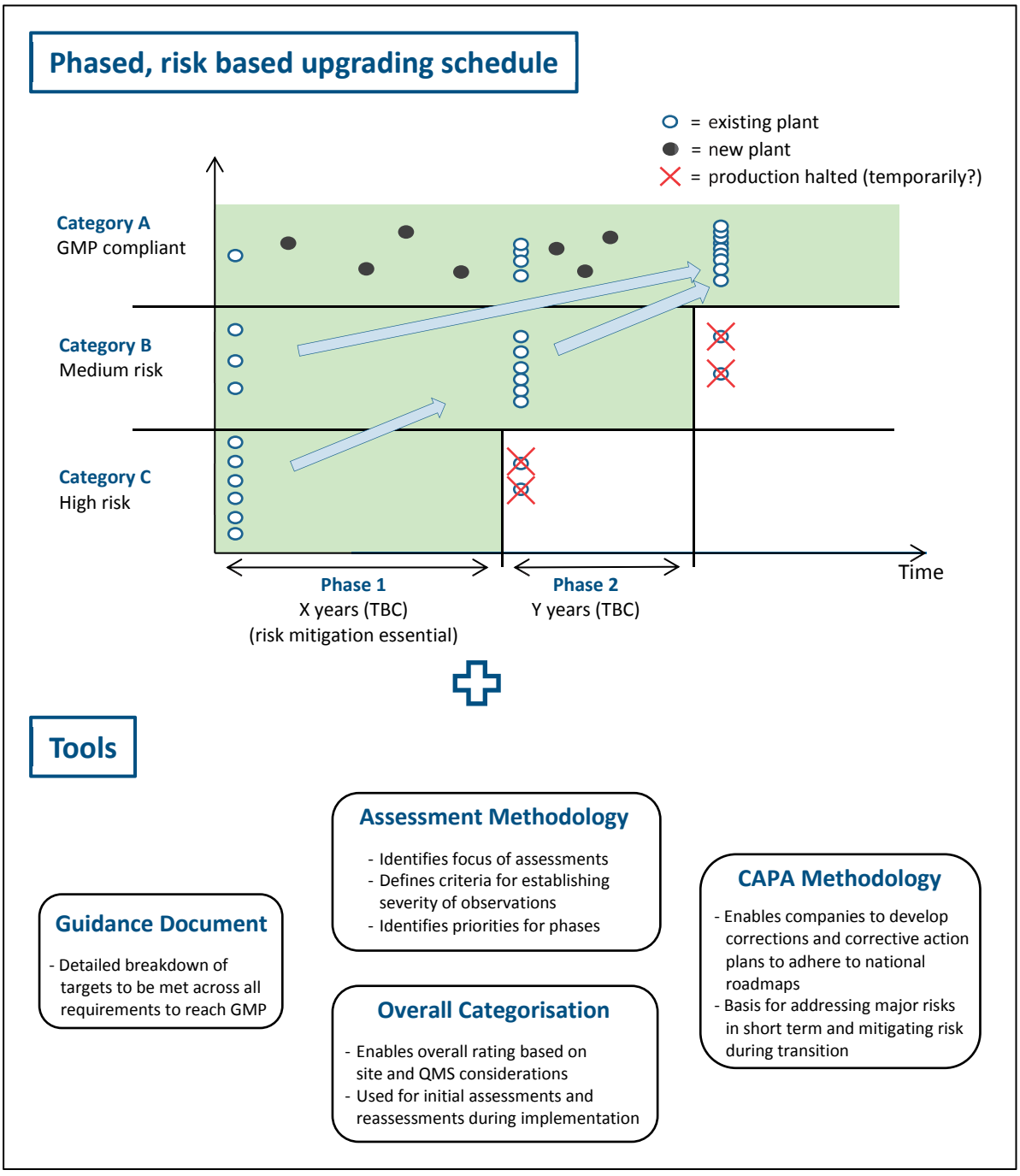
The framework consists of tools and guidance as well as a risk based phased schedule for upgrading standards (see below for schematic representation). It includes the following tools and guidance:

- 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.)
2. Risk based approach where the technical deficiencies that pose the most significant threat to safety are addressed first.
3. Measures for risk mitigation during the transition towards WHO GMP standards.
4. The requirement that all new facilities meet WHO GMP standards before they are licensed for manufacturing.

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 November 2018 at the Third Regional Workshop, held in Abidjan, Ivory Coast. The workshop was 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 such as the United States Pharmacopeia (USP) and the African Development Bank (AfDB). The meeting was chaired by the President of the West African Pharmaceutical Manufacturers Association.

Key benefits of a framework approach for the upgrading pharmaceutical manufacturing standards in the region

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;
- More advanced manufacturers can reach international standards in the relatively near term, a key requirement for accessing the international donor markets;
- Risk to public health can be mitigated whilst manufacturers upgrade to international standards.

Considerations for implementation

This document is a reference document. A detailed implementation plan is required to enable manufacturers across the region to adhere to these requirements and for stakeholders to support, require and monitor progress. Furthermore, other dimensions of access (e.g. affordability, availability, accessibility etc.) need to be properly addressed. Section 9 touches on some of these issues as a means to highlight the importance of such an implementation plan to realise the technical objectives of this framework and the associated national GMP roadmaps such that the vision of the ERPP can be achieved.

1 INTRODUCTION

In 2015 the Heads of State of the Economic Community of West African States (ECOWAS) endorsed the ECOWAS Regional Pharmaceutical Plan (ERPP). This was developed by the West African Health Organization (WAHO), which was established as specialized agency in 1987. The organization's mission is as follows:

"*The Objective of the West African Health Organization shall be the attainment of the highest possible standard and protection of health of the peoples in the region through the harmonization of the policies of Member States, pooling of resources and cooperation with one another and with others for a collective and strategic combat against the health problems of the region"*.

The ERPP document explicitly recognizes that health systems rely on the continuous availability of safe, affordable pharmaceuticals of assured quality and that delivering on this need would be greatly enhanced through developing the pharmaceutical manufacturing industry within the region. The ERPP is a forward looking document that establishes a long term vision for pharmaceuticals in the region, acknowledging the benefits that proximity of production to point of use has with regard to sustainability of supply. It sets a target of increasing locally manufactured pharmaceuticals from 30% to 60%.

The document sets out a comprehensive approach to developing the pharmaceutical sector in the region to contribute to improved public health and the economic development of the region. With a key objective being to support the local industry to develop, not only to provide for the region's needs, but also to be a source of high quality exports. The mission of the ERPP includes:

"*The ECOWAS Regional Pharmaceutical Plan 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".*

Adherence to international Good Manufacturing Practice (GMP) is essential to ensure quality, safety and efficacy of medicinal products. However, GMP involves a vast array of requirements, which can be overwhelming for manufacturers that are not familiar with them, particularly when coupled with the significant investment that is required in both time and financial resources, not to mention the detailed expertise involved.

WAHO has recognized the need to apply internationally accepted GMP standards for manufacturers in the region, but acknowledges that this cannot happen overnight and that a structured approach that supports manufacturers to reach this objective is required. It is also acknowledged that the pharmaceutical manufacturing sectors in West Africa are highly heterogeneous, not least in terms of size, with Nigeria having well over 100 active manufacturers, Ghana at least 25, and other countries between 0-4 manufacturers. This heterogeneity means that specific technical and policy solutions need to be developed for each Member State to ensure that manufacturing of pharmaceuticals adheres to GMP. However, it is also necessary that an overarching regional framework is in place, to which all Member States subscribe, setting out the fundamental requirements for upgrading the industry to international standards over a defined period of time. In this way a consistent approach can be applied across the region, which not least will contribute to the ongoing regulatory

harmonization process and ensure that companies can benefit from the cost efficiencies that can be achieved through access to larger markets.

Hence WAHO, in collaboration with the United Nations Industrial Development Organization (UNIDO) undertook an assessment and diagnostic process to determine current manufacturing standards across the region, with a view to develop GMP Roadmaps for each Member State. The process also involved developing this Regional Framework that ensures that all Member States can develop their existing capacity and/or develop new capacity that meets the requirements of international GMP based on a common approach across the region.

This Regional GMP Roadmap Framework for ECOWAS member states was validated in November 2018 at the Third Regional Workshop, held in Abidjan, Ivory Coast. The workshop was 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 such as USP and the AFDB. The meeting was chaired by the President of the West African Pharmaceutical Manufacturers Association.

2 OVERARCHING CONSIDERATIONS FOR THE DEVELOPMENT OF THIS FRAMEWORK

Adherence to Good Manufacturing Practice (GMP) is essential to ensure quality, safety and efficacy of medicinal products. In order to support pharmaceutical manufacturers within the ECOWAS region during their development towards WHO GMP compliance, a technical framework has been developed defining approaches and activities that have been applied at the country level to provide guidance for development of the industrial pharmaceutical manufacturing sector towards compliance with WHO GMP standards. The framework presented in this document should be understood as a master document describing the approach that enables consistency in philosophy, approach and requirements that national level roadmaps can adhere to.

The approach for development of finished pharmaceutical product (FPP) manufacturers towards WHO GMP recognizes the need for risk mitigation during transition from current manufacturing practices to full compliance with WHO GMP. This framework also includes tools for standardization of methodologies for categorization of FPP manufacturers according to their compliance with WHO GMP. Central to the framework is the technical Annex which identifies specific activities and milestones for implementation of key quality elements that need to be addressed during the pathway from current manufacturing practices towards WHO GMP. Furthermore, this document describes approaches for mitigation of production and product related risks during implementation of this framework.

3 METHODOLOGY

In order to develop the national GMP roadmaps and a regional framework a robust, scientifically sound methodology was utilised. Critical components of this methodology were:

- Determining the reference GMP standards on which this work is based;
- Defining the scope of the framework and hence the scope of the national level roadmaps;
- Conducting base line assessments on the level of GMP compliance across the region based on standardized tools for data collection to identify key technical challenges, and rating of observations and overall compliance to GMP;
- Developing a GMP roadmap framework that is relevant to all countries in the region;
- Including means to mitigate risk during the transition to GMP compliance.

3.1 GMP reference standard

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.

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 the ECOWAS region strive to achieve compliance with WHO GMP, since this forms part of the requirements for having their products prequalified by WHO.

3.2 Scope of the framework

The scope of this 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 products;
- Pharmaceutical manufacturers other than manufacturers of finished pharmaceutical products such as distributors, importers, wholesalers, raw materials manufacturers, packaging material manufacturers.

3.3 Baseline assessments

The number of active pharmaceutical manufacturers varies dramatically across the region. It should be noted that UNIDO had already conducted baseline assessments of all manufacturers in Ghana. Apart from Nigeria, all other countries have up to four manufacturers that fall within the scope of the framework. All of these manufacturers were assessed as part of this project.

In Nigeria there are an estimated 182 active pharmaceutical manufacturers. In order to gather data in a timely manner, a representative sample of these manufacturers needed to be incorporated. To achieve this, a sampling methodology was developed to ensure that a representative cross section of manufacturers was covered as part of the baseline assessment. The tool was based on the National Agency for Food and Drug Administration and Control (NAFDAC) assessments of GMP compliance, ensured that different geopolitical zones were covered and that different product forms were included. Having categorized companies based on these different criteria companies were invited to volunteer to take part in the assessments. In total 25 companies were assessed.

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.

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.

3.4 Development of CAPAs

Following the assessments, each company received a report on the findings. Based on these findings and following training on development of corrections and corrective action plans (CAPAs), companies

developed CAPAs to address the gaps that were found. Guidance on how to refine these plans was provided by the GMP experts working on behalf of UNIDO. All companies assessed now have CAPAs that should be the basis for their development. The issue of additional assessments and CAPA development for Nigeria is covered in the National GMP roadmap (volunteer companies have received support in developing CAPAs). At the company level it is these CAPAs that establish the technical approach for meeting the requirements to upgrade towards international GMP.

3.5 Rating of observations

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

3.6 Identification of technical challenges based on the outcome of assessments performed

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

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

This tool provides a measure of the compliance of the manufacturer 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 (≤ 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.

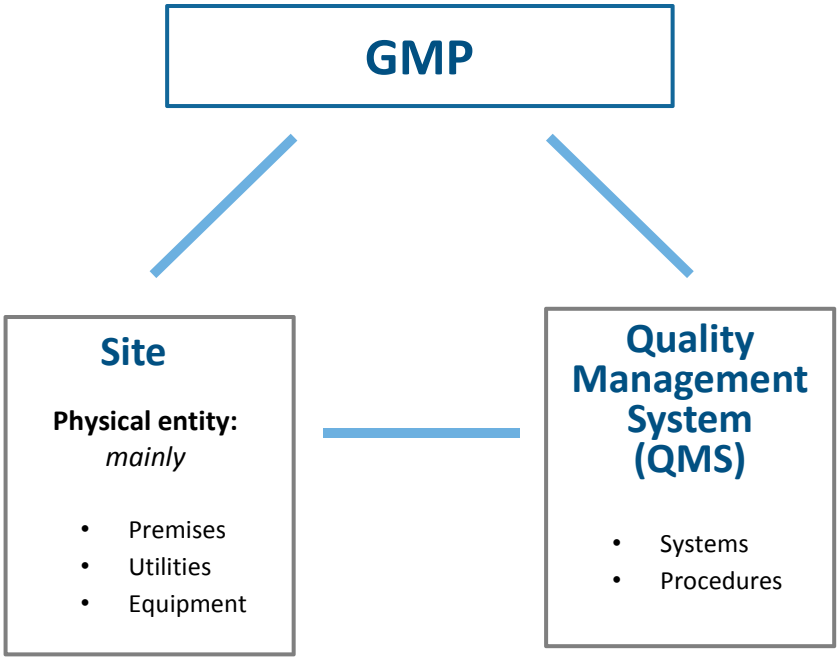
3.6.2 Tool 2: Categorization of a FPP manufacturer's overall compliance with WHO GMP

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 1.

Figure 1: 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 2 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.

Figure 2: Risk 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**

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 for identifying main technical challenges and the risk associated to manufacturing activities by individual manufacturers the tool also allows for prioritization and streamlining of CAPA activities. Hence, the categorization of FPP manufacturers according to their WHO GMP compliance is a key tool of this framework.

4 RESULTS OF BASELINE ASSESSMENTS

4.1 Break down by overall classification

In total (including the assessments conducted in Ghana) 67 companies were assessed of which 64 could be graded according to their compliance to international GMP. The majority of companies are currently C rated with a significant minority rated as B and a small proportion as A.

The baseline assessments revealed that the majority of companies face significant gaps between their current manufacturing practices and requirements for GMP. Addressing these gaps takes time and the focus must be on addressing issues that pose the highest risk to product safety first. Hence the Regional GMP roadmap framework utilizes a risk based phased approach for existing companies to move from current manufacturing practices to being in compliance with WHO GMP. The assessments have revealed that the key technical challenges where most significant gaps are to be found do vary across the different countries.

The baseline assessments hence reveal that there are significant site related issues that need to be addressed as well as QMS considerations. Whilst expertise, resources, management commitment and other factors are required to address both site and QMS dimensions, major retrofitting of existing facilities or design and construction of new facilities require significant time.

4.2 Implications of baseline assessments for the Regional GMP Roadmap Framework

The baseline assessments revealed that the majority of companies within the sample were categorized as being high risk, a significant proportion were medium risk and at least two companies within the sample were found to be largely compliant with WHO GMP.

These results have come from assessments in all countries where active manufacturing was occurring at the time of the assessment. These are shown in table 1.

In addition to the technical assessments, country consultations took place with all member states in part to ascertain the interest in establishing and/or expanding their pharmaceutical industries. It was found that a number of countries intend to expand their pharmaceutical sectors. In addition, two countries have a keen interest in establishing/reinitiating pharmaceutical manufacturing in the near term, with others considering their options subject to further developments. However, even countries that have no imminent interest in domestic production recognized that enhanced manufacturing within the region would be a major improvement as it would help them to tackle the scourge of substandard and counterfeit products.

Table 1: Number of active pharmaceutical companies assessed

Country	Number of companies
Benin	1
Cabo Verde	1
Cote d'Ivoire	4
Guinea	1
Ghana	26*
Mali	2
Nigeria	25**
Senegal	2
Togo	2

* Under another UNIDO project an initial roadmap for Ghana was developed and during implementation all active pharmaceutical manufacturers were assessed

** Indicates a representative sample was assessed

The findings from the technical assessments and country missions indicate that the regional framework must provide:

1. Comprehensive technical guidance to meeting GMP requirements across all sub-components of the 17 key quality elements (see Appendix 1).
2. A risk based phased approach for upgrading existing manufacturers with defined timelines that companies should adhere to upgrade to be largely in line with WHO GMP (and for high risk companies to achieve medium risk in the interim).
3. A consistent methodology for categorizing the level of GMP compliance of companies including for reassessing as the roadmaps are implemented.
4. Agreement that all new companies should meet GMP requirements prior to receiving a manufacturing license, and a checklist of considerations that can be used by regulators as a point of reference.
5. Measures to mitigate the risk to product safety during the transition to WHO compliance, particular for those currently rated C.

5 DEVELOPING A FRAMEWORK THAT IS RELEVANT TO ALL COUNTRIES: THE RISK-BASED, STEPWISE APPROACH TOWARDS WHO GMP

The context for manufacturing varies dramatically between Member States and companies across the region are currently operating at significantly different levels of compliance with GMP. In order to ensure that the pathway for the transition from current manufacturing practices to compliance with WHO GMP is achievable and scientifically sound, a risk-based and phased approach for development of local manufacturing practices towards compliance with WHO GMP has been utilised, taking into account the outcomes of GMP assessments performed.

All manufacturers assessed were categorized according to their compliance with WHO GMP utilizing "Tool 2: Categorization of a FPP manufacturer's overall compliance with WHO GMP" as outlined in above. This tool defines three risk categories of FPP manufacturers based on their compliance with WHO GMP, namely:

- Category "A": Approach towards pharmaceutical manufacturing in general in line with WHO GMP → **Low risk manufacturer**
- Category "B": Approach towards pharmaceutical manufacturing not in line with WHO GMP but reduced risk with regards to production safety → **Medium risk manufacturer**
- Category "C": Approach towards pharmaceutical manufacturing not in line with WHO GMP and high risk with regards to production safety → **High risk manufacturer**

As this tool defines three risk categories, two phases are required for a step-wise improvement from category "C" to category "A":

- Phase I providing guidance during the transition from category "C" to category "B" and
- Phase II providing guidance during the transition from category "B" to category "A".

5.1 Foci of the phases for stepwise improvement from current manufacturing practices to compliance with WHO GMP

5.1.1 Focus of Phase I

During the improvement from category "C" to category "B" the initial focus needs to be on mitigating immediate risks caused by serious non-compliances with WHO GMP in the short to medium term in order to allow for a step-wise improvement from current practices towards WHO GMP. Risk mitigation has to be done at the manufacturer level within the guidance provided by the national GMP roadmap and is hence in line with the regional framework. Once immediate risks are mitigated, it is essential to focus on the improvement of those main technical challenges that have the highest impact on quality, safety and efficacy of the medicinal products manufactured. Hence, this should be the focus of Phase I.

The baseline assessments performed as part of this project and those conducted for development and implementation of the Ghana GMP Roadmap have highlighted that a typical reason for low levels of overall GMP compliance were site related GMP deficiencies. As the modification of existing sites or even the construction of a new manufacturing site are highly time consuming activities due to the construction processes and the need to secure sufficient financial resources to fund the project, such modifications or construction of sites should be started at an early stage of the stepwise pathway to WHO GMP compliance and hence should be addressed as part of the Phase I activities.

The focus of Phase I can be summarized as follows:

- Mitigation of risks caused by serious non-compliances with WHO GMP
- Improvement / Implementation of key quality elements to which manufacturers showed least compliance often involving construction / modification of sites to adhere to WHO GMP requirements

Using the above approach, FPP manufacturers which have been rated initially as category "C" should reach a "B" rating at the end of phase I, as site related deficiencies should no longer pose a high risk to production safety and at least a sporadically implemented QMS should be in place.

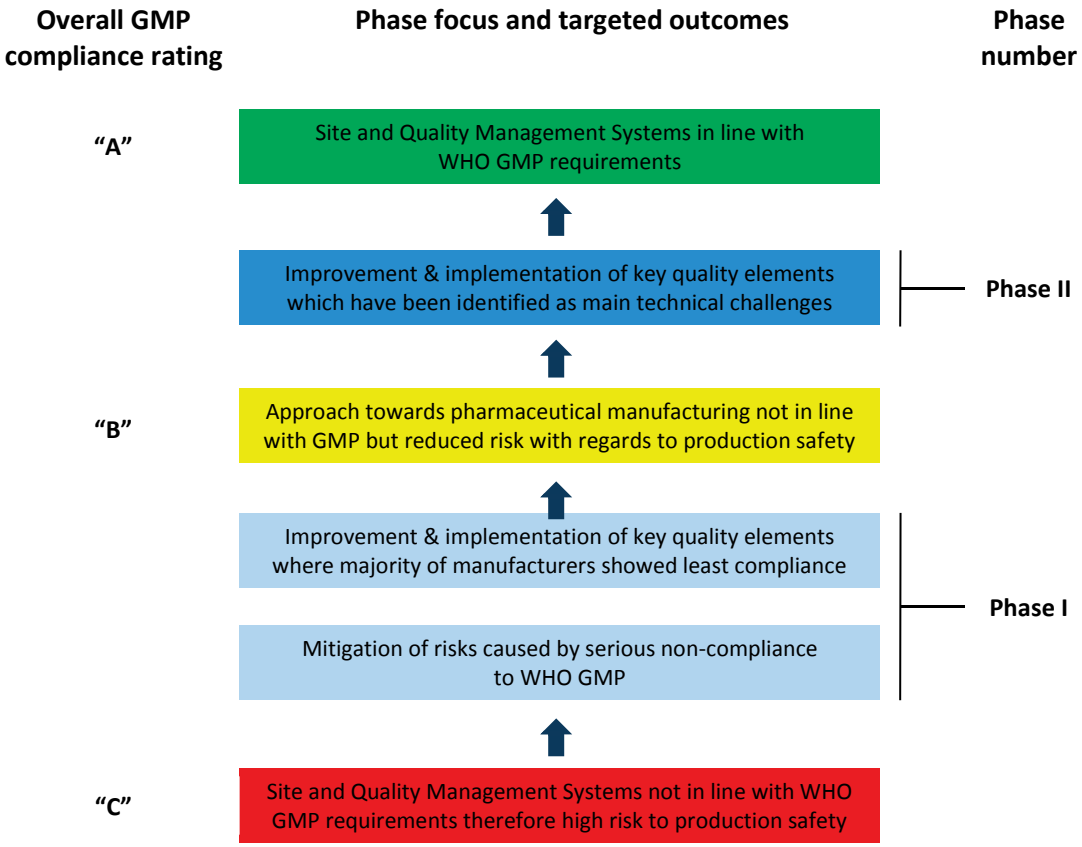
5.1.2 Focus of Phase II

During Phase II which involves transition from category "B" to category "A", the focus will be on achieving comprehensive compliance with WHO GMP by addressing those GMP aspects which have not been covered during Phase I. This means that Phase II of the GMP Roadmap framework (and as applicable the national level roadmaps) will focus primarily on those key quality elements which have not been identified as main technical challenges and hence have not been addressed during Phase I. After completion of Phase II, both structural ("site") and organizational measures ("QMS") will meet the requirements, hence the FPP manufacturers will be operating in line with WHO GMP.

This risk-based, stepwise approach towards full WHO GMP compliance is graphically displayed in figure 3. The definition of the individual phases of the GMP Roadmap is based on the severity of deficiencies from WHO GMP and on the compliance risk attributed to pharmaceutical manufacturers in the region. Hence this framework includes risk mitigation and a stepwise approach that form the central pillars that are tailored for the specific roadmap requirements at the national level.

This stepwise, phased pathway towards compliance with WHO GMP allows for a flexible approach taking into considerations the different levels of WHO GMP compliance of FPP manufacturers within a specific country. The risk category assigned to the individual manufacturer allows each manufacturer to identify the entry level into the GMP roadmap and hence the number of phases to be completed in order to achieve compliance with WHO GMP. In this context it has to be pointed out that FPP manufacturers entering this phased pathway as category "B" should evaluate the need for mitigation of immediate risks caused by non-compliances with WHO GMP until adequate corrections and corrective actions are implemented.

Figure 3: Risk-based, phased pathway towards achievement of full WHO GMP compliance



5.2 Country variation in applying the framework

As discussed previously this framework has been developed to cover the substantial variations between the sectors of different member states and the resultant different types of roadmap that have been developed at the national level. The following table gives a brief description of the difference between the situations encountered.

Table 2: Overview of different scenarios for applying the strategic components according to the extent of pharmaceutical manufacturing activity within a country

Step	Countries with no FPP manufacturers	Countries with up to 10 FPP manufacturers	Countries with more than 10 FPP manufacturers
Baseline assessment of manufacturers	Not applicable	Assessment of all FPP manufacturers	Assessment of a representative sample of manufacturers
Identification of technical challenges	Not applicable	Performed for each individual manufacturer	Performed initially for a representative sample of manufacturers Application of tools to identify main technical main challenges within the country Verification of identified main technical challenges during implementation phase of guidance document
Contents of GMP roadmaps	GMP roadmap provides guidance on how to establish GMP compliant manufacturing prior to plant operations given specific national level technical considerations	Each manufacturer assessed to develop baseline. Roadmap based on findings and the CAPA's developed for each company. Guidance on establishing new facilities compliant with GMP	Development of comprehensive country-specific roadmaps towards WHO GMP detailing the pathway for the transition from current manufacturing practices to WHO GMP compliance for ALL FPP manufacturers within the scope of this project Volunteer companies in Nigeria assisted to develop CAPAs Implementation involving assessment and support to develop CAPAs for all active manufacturers requiring that any start-up FPP manufacturer will have to comply with WHO GMP in order to be licensed for manufacturing

5.3 Manufacturer entry points

5.3.1 Entry point for category C manufacturer

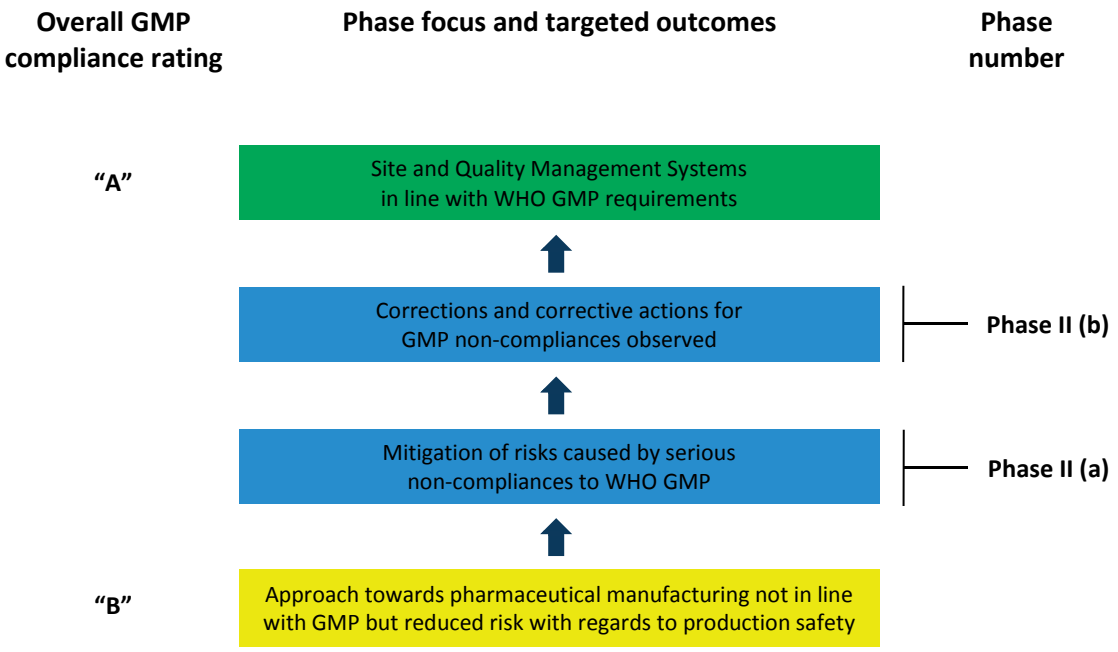
As the assessments have shown at the time of site visits, manufacturers were operating at different levels of compliance with GMP. Hence different companies start at different points. The specifics are highlighted in greater detail in individual country roadmaps. However, companies can initially be categorised as C, B or A. Those categorised at C start at phase 1.

5.3.2 Entry point for category B manufacturer

FPP manufacturers which have been rated initially as category "B" are not operating in line with WHO GMP but despite the GMP non-compliances observed the approach towards manufacturing does not lead to a high risk with regards to production safety. As the FPP manufacturer already operates in category "B", no Phase I is necessary. The manufacturer will have to complete Phase II in order to achieve compliance with WHO GMP. In such a scenario Phase II should be subdivided into an initial Phase II (a) which will focus on mitigation of any production related risks and Phase II (b) which will focus on corrections and corrective actions for GMP non-compliances observed ensuring compliance with WHO GMP and hence improvement towards category "A" is achieved.

The risk-based, phased pathway for the manufacturer-specific approach towards WHO GMP compliance for FPP manufacturers which have been rated initially as category "B" is graphically displayed in figure 4.

Figure 4: Risk-based, phased pathway towards achievement of full WHO GMP compliance – FPP manufacturers rated initially as category "B"



5.3.3 Entry point for category A manufacturer

FPP manufacturers which have been initially rated as category "A" as outcome of the GMP assessment performed are operating in line with WHO GMP. Hence, there should typically be no need for initial risk mitigation. No Phase I and Phase II can be defined for these plants. Nevertheless, the FPP manufacturers will be required to prepare corrections and corrective action to the extent needed for deficiencies observed during assessments.

6 TECHNICAL GUIDANCE TOOL FOR THE GMP KEY QUALITY ELEMENTS

A tool to provide guidance on the technical specifics for each of the 17 key quality elements based on WHO GMP requirements and typical deficiencies observed during assessments has been developed. For each key quality element this tool defines actions and milestones for implementation, separating out those that pertain to site related and QMS related aspects of GMP.

The technical specifics of this guidance tool are outlined in the Annex of this framework.

The tool provides guidance regarding the development of, and implementation requirements for, site and quality management systems in line with WHO GMP. The technical specifics detailed for each key quality element should be read in conjunction with respective WHO GMP guidelines. The technical specifics can be utilized by FPP manufacturers and regulatory authorities on the path towards WHO GMP as follows:

I. Existing manufacturers

Already existing FPP manufacturers can use the guidance tool together with the tools provided for assessment and evaluation of assessment results in section 4 of this framework in order to perform a gap analysis between their current and aspired compliance with WHO GMP requirements, and to follow a phased approach towards closing the gaps identified.

II. New manufacturers

New start-up FPP manufacturers can use this guidance tool to ensure that all necessary elements and systems are taken into consideration, and to check that site and QMS related GMP aspects are in line with WHO GMP requirements before applying for licensing by the regulatory authority.

III. Regulatory authorities

The regulatory authority can use this guidance tool to review licensing criteria for new and existing facilities in order to improve them gradually until they are in line with WHO GMP requirements.

7 RISK MITIGATION

A core aspect during implementation of this framework for developing FPP manufacturers within the ECOWAS region towards WHO GMP standards is risk mitigation during the transition of already operational manufacturers from existing manufacturing practices to full compliance with WHO GMP. During the transition from current manufacturing practices to compliance with WHO GMP two different types of risk need to be considered:

- Production related Risks, and
- Product related Risks

Production related risks are risks caused by the non-compliances with WHO GMP which at worst case can impair production safety.

Product related risks are risks attributed to the nature of certain dosage forms and products which include risk factors such as complexity of manufacturing processes, the risk of losing control during manufacture, the risk of products causing or being susceptible to contamination and cross-contamination, the therapeutic range, required storage conditions, availability of specifications and material and product characteristics such as solubility, the exhibition of polymorphism, the bio-chemical classification of active pharmaceutical ingredients and stability considerations.

7.1 Considerations for mitigation of production related risks

Manufacturers are required to prepare corrective action plans for the GMP non-compliances observed. One of the key aspects during preparation of these corrective action plans is mitigation of risks arising from the deficiencies observed. For the majority of FPP manufacturers the transition from current manufacturing practices to compliance with WHO GMP is expected to be a time-consuming process. Especially in cases where the implementation of corrections is not possible for serious deficiencies within a reasonable timeframe as e.g. structural modifications to the site or the establishment of entire quality management systems are required, the manufacturer will have to define and implement adequate actions to mitigate identified risks until adequate corrections and corrective actions for the deficiencies are implemented. This need for initial mitigation of risks is a key pillar of the risk-based approach delineated in section 5 of this document. FPP manufacturers should only be allowed to continue manufacturing during their transition from current practices to compliance with WHO GMP, where adequate measures to mitigate production related risks during this transition have been implemented. Besides, FPP manufacturers will have to ensure that their corrective action plans adhere to project timelines and milestones as determined for the implementation of this framework and national GMP roadmaps.

Another aspect for mitigation of production related risks during the implementation of this framework is the risk-based, stepwise approach itself which is utilized in this framework. This ensures throughout that the most serious deficiencies are addressed in the initial phase, as they have the highest impact on production safety: Corrections and corrective action for the most serious deficiencies observed are typically addressed in the initial phase, as applicable.

7.2 Considerations for mitigation of product related risks

During the transition of already operational FPP manufacturers from existing manufacturing practices to compliance with WHO GMP, besides production related risks, those associated with the nature of product need to be considered as part of the risk mitigation strategy. Product related risks vary for product categories and individual products and both dimensions should be considered if and when manufacturing restrictions are applied.

Such an approach could be based on the risk categorization of manufacturers as outlined for "Tool 2" in section 4 of this document and the risk classification of essential medicines performed by WHO[1,2]. Thereby the GMP compliance risk category of a manufacturer could be a basis for mitigating product related risk during transition from current manufacturing practices to full WHO GMP compliance. Such an approach could be based on WHO's document[2] which describes a methodology for determining a risk level for the "Potential loss of state of control" and for the "Contamination risk based on product form".

The risks associated to individual products within these categories vary significantly, for example due to the complexity of the required manufacturing process, the therapeutic range, storage conditions, availability of specifications, etc. Hence the above can form a basis for identifying product related risk but it is necessary to apply more variables to fully reflect the inherent risk at the product level.

The issue of mitigating product risk and applying policies and tools to achieve that end is both highly technical and needs to take into account the strategic context. There are potential collateral benefits, given that through identifying "High risk products" for which sufficient quality assured capacity is in place within the region (for example), a significant incentive to upgrade to GMP standards could be established to restrict manufacturing to those companies that meet the requisite standards. However, such an approach needs very careful consideration as to the ramifications and potential unforeseen consequences. Therefore, detailed assessment and scenario analysis needs to be applied in developing any such methodology for use during the implementation of the roadmap framework. Furthermore, close alignment and collaboration with other WAHO led initiatives; in particular the Medicines Regulatory Harmonization initiative would be warranted. Product related risk could be addressed through specific regulatory guidance rather than the broader industrial development issues that will need to be addressed in implementing this framework and associated national level roadmaps.

[1] World Health Organization. Concept paper for discussion. A framework for risk-based identification of essential medicine products for local manufacturing in low- and middle-income countries. WHO Drug Information. Vol. 30, No. 2, 2016.

[2] World Health Organization. A risk-based identification of essential medicines for local manufacturing in low- and middle-income countries. Working document QAS/16.682. Draft document for comment. August 2016.

8 STRATEGIC CONSIDERATIONS FOR IMPLEMENTATION OF THE REGIONAL GMP ROADMAP FRAMEWORK

This is a technical reference document that sets out the Regional Framework under which national level GMP roadmaps will be implemented. Operationalisation of this roadmap requires numerous strategic considerations to be taken into account. For example the industry will require a package of support to enable it to invest in upgrading manufacturing operations and to access the expertise to conduct this work as well as sustainably operate the facilities at internationally recognized standards. There are many other areas of support that will need to be considered for the industry and associated stakeholders.

However, perhaps the most critical issues that need to be addressed relate to reaching consensus between member states on aspects of the roadmap itself and the degree to which ECOWAS Member States can move towards a single market for pharmaceutical products.

For example, the framework establishes a two phased approach to developing the sector. It is necessary to set deadlines for the completion of each phase. Typically phase 1 would take 3-5 years and phase 2 should be completed within a further 2 years. However the vast differences between countries suggest that some could achieve full compliance relatively quickly whilst others will require much longer. This may also be a key consideration for non-manufacturing countries given that they might perceive that their putative industries (which should be GMP compliant from the start) would be at a disadvantage (subject to performance related incentives that might be considered) until all manufacturers are required to operate according to GMP.

The nature of the incentives that countries can provide to support manufacturers will also have to be considered and perhaps ranges and types defined to avoid overly benefitting the sector in particular countries whilst also enabling all manufacturers 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.

Similarly 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 curtailed 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 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 should be considered 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.

On finalisation of this framework and the national level roadmaps an implementation plan will need to tackle these issues and others. Hence the realisation of the benefits that would accrue from

achieving the objectives of this framework will require a long term, detailed, well-resourced implementation plan.

9 SUMMARY OF FRAMEWORK

This framework consists of different tools and a phased, risk based upgrading schedule. It is summarised graphically in figure 5 below.

The tools include:

- 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

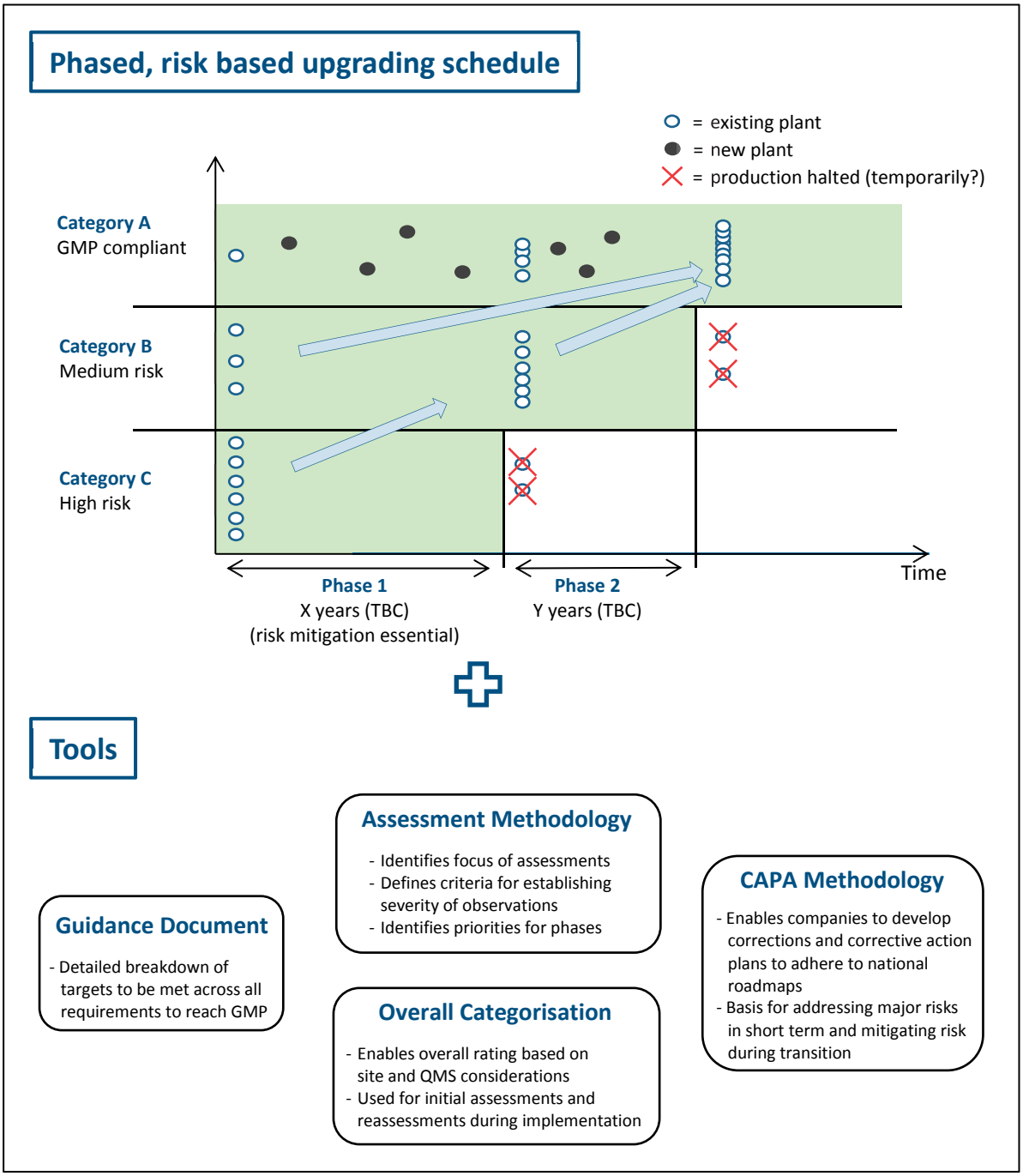
The phased, risk based schedule involves the following:

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.)
2. Risk based approach where the technical deficiencies that pose the most significant threat to safety are addressed first.
3. Measures for risk mitigation during the transition towards WHO GMP standards.
4. The requirement that all new facilities meet WHO GMP standards before they are licensed for manufacturing.

Through methodical and comprehensive implementation these components provide a basis by which:

- Industries across the region can follow a unified approach to upgrading and ultimately reaching WHO GMP.
- More advanced companies can reach international 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 recognized standards.

Figure 5: Schematic representation of the key components of the Regional GMP Roadmap Framework



APPENDIX I: KEY QUALITY ELEMENTS AND FOCUS OF ASSESSMENTS

WHO GMP requirements have been defined in 17 key quality elements. In table 3, each of these is broken down into sub-sections for which the assessment focus has been defined.

Table 3: Key quality elements, defined subsections and focus during assessment

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

Key quality elements	Subsections	Focus during assessment

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

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

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

Key quality elements	Subsections	Focus during assessment
2. Utilities impacting GMP requirements (ctd.)	Water system	• Feed water quality • Water quality(ies) being used within the plant and purpose of use • Suitability of construction materials and purification steps used • Welding • Slope of pipeworks, drainability • Labelling of pipeworks • 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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX II: ASSESSMENT SCHEDULE FOR SITE VISIT

Based on defined key quality elements of WHO GMP and assessment focus areas, an assessment schedule has been prepared. This is uniformly applied to assess manufacturers of finished pharmaceutical products within the ECOWAS region in terms of their existing level of compliance with WHO GMP. Each manufacturer is assessed for two full working days. This assessment schedule is displayed in table 4.

Table 4: Assessment schedule for the gap analysis of pharmaceutical manufacturers regarding their existing level of compliance with 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 rowspan="2">Factory tour:
Warehouses
Receiving area and stores
Starting and packaging materials
Sampling and issuing
Production
Utilities with direct impact on product quality, such as
HVAC system
Water system
Compressed air system</td></tr>
</table>

<table>
<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
• Personal hygiene
• Product quality review
• Self-inspections
• Corrective and preventive action (CAPA) procedures
• Rework/Reprocessing procedure
• Quality risk management
• Review of additional documents</td></tr>
<tr><td>Wrap up and summary of findings

Closing of meeting</td></tr>
</table>

APPENDIX III: GUIDANCE FOR RATING RISKS RELATED TO "SITE" AND "QMS" NON-COMPLIANCE

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

Table 5a: Indicator criteria for site-related risk levels.

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

The overall site rating (1, 2 or 3) should be selected so as to best reflect the ratings assigned to the individual site attributes.

Table 5b: Indicator criteria for QMS-related risk level

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

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; material qualities are defined for all materials and in line with GMP requirements; materials used for pharmaceutical manufacturing are of acceptable quality; materials used for operations such as cleaning, lubrication and pest control are in line with GMP requirements	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; material qualities are defined for some but not for all materials; materials used for pharmaceutical production are fit for human consumption although GMP deficiencies regarding their quality are observed; although GMP deficiencies regarding the materials used for cleaning, lubrication and pest control are observed, these materials do not cause a serious health hazard	No testing of materials/products is performed; procedures for receipt, sampling, storage, manufacturing and distribution are inadequate; no related GMP documentation is in place; material qualities are in general not defined; quality of materials used for pharmaceutical production is unfit for human consumption; materials used for cleaning, lubrication and pest control are inadequate for their use and cause a serious health hazard
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

The overall QMS rating (1, 2 or 3) should be selected so as to best reflect the ratings assigned to the individual QMS attributes.

ANNEX: GUIDANCE TOOL PROVIDING TECHNICAL REQUIREMENTS OF EACH KEY QUALITY ELEMENT

The GMP reference standard for this framework is the 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. In order to provide further guidance on the technical specifics for each of the 17 key quality elements, a tool has been developed, based on WHO GMP requirements and typical deficiencies observed during assessments performed in the ECOWAS region as part of this project, defining for each key quality element actions and milestones for implementation. Furthermore, for those key quality elements that address both site and QMS related GMP aspects, the required improvement measures and milestones presented are broken down according to these two dimensions.

The technical specifics of this guidance tool should be read in conjunction with the respective WHO GMP guidelines.

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

Reference number	Key quality element	Actions for implementation	Milestones
2.	Utilities impacting Good Manufactur-ing Practice	**Site related aspects:** Water: Identification of the required water qualities needed for the operations to be performed at the site Identification of a water source suitable for the production of potable and purified water. Definition of (pre-) treatments required of the source water to obtain water in potable and purified quality. 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. Establishment of suitable supplier(s)* for components of water treatment plant. Installation/Commissioning of the water treatment plant and distribution system complying with the design specifications.	**Site related aspects:** Required water qualities needed for intended operations identified Suitable water source (e.g. borehole or public water) identified. Quality of source water identified. Requirements for water treatment defined. Design specifications and layout of water treatment plant available. Position of sampling points defined and identified. Suitable supplier(s) identified and contracts available. Water treatment plant and distribution system complying with predefined specifications and design in place. As-built system conforms to

Reference number	Key quality element	Actions for implementation	Milestones
			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 becoming cross-contaminated and contaminated, as well as preventing 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 the 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 with 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

Reference number	Key quality element	Actions for implementation	Milestones
			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 with 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 with the design specifications.	Steam generation and distribution system(s) complying with

Reference number	Key quality element	Actions for implementation	Milestones
			predefined specifications and design in place. As-built system conforms to original design drawings.
		QMS related aspects:	**QMS related aspects:**
		Development and implementation of a system containing documented procedures, protocols, reports and records for calibration, qualification, maintenance, cleaning and sanitization for each equipment.	System containing documented procedures, protocols, reports and records for calibration, qualification, maintenance, cleaning and sanitization for each equipment in place and implemented.
		Development and implementation of documented procedures for operation of equipment including records/logbooks for each piece of 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, sampling frequencies and test methods in place and implemented.

Reference number	Key quality element	Actions for implementation	Milestones
		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.
3.	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. 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 a routine environmental monitoring program including specifications, action and alert limits, sampling procedures and frequencies for evaluation.	Suitable cleaning procedures developed and successfully validated. A comprehensive cleaning program including schedule and logs is in place and followed. Routine environmental monitoring programs are developed and implemented.
4.	Qualification and validation	Development and implementation of master documentation for calibration, qualification and validation activities (Validation master plan and Project plans) outlining approach (risk-based), procedures, responsibilities, schedules, management of all lifecycle stages and documentation requirements. Development and implementation of plans, protocols and reports for calibration, qualification and validation procedures including documented procedures, plans and reports for (re-)calibration, (re-)qualification and (re-)validation of buildings, utilities, equipment, controls, processes and methods as outlined in the validation master plan. Development and implementation of systems for review and tracking of calibration, qualification and validation status.	Master documentation in place and implemented. Plans, protocols and reports for (re)-calibration, (re-) qualification and (re-) 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.

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

Reference number	Key quality element	Actions for implementation	Milestones
		knowledge management, attributes impacting quality or traceability 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	
8.	Self-inspection, quality audits and suppliers' audits and approval	Development and implementation of a system for self-inspections including • Inspection program • Inspection frequency • Composition of inspection team, training requirements and responsibilities • Record and classification of audit observations • Reporting of observations • Corrections and corrective actions • Evaluation of effectiveness of actions taken Development and implementation of a system for manufacturer and supplier audits and approval including • Procedure and criteria for evaluation of 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 and disqualification of manufacturers and suppliers, for those where no audit need has been identified • Definition of qualification and disqualification criteria for manufacturers and suppliers, and related procedures • Requirement to establish quality/technical agreements with manufacturers and suppliers • A list of approved manufacturers and suppliers for starting and packaging materials • Procedure, criteria and periods for monitoring and re-evaluation/re-qualification of manufacturers and suppliers of starting and packaging materials	Self-inspection procedures developed and implemented. Procedures for manufacturer and supplier qualification in place and implemented.
9.	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	Number, qualifications and experience of personnel defined. Signed and dated job descriptions for personnel in place.

Reference number	Key quality element	Actions for implementation	Milestones
		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.	Mechanisms and procedures in place and implemented for restriction of access.
10.	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 records including their review and update procedures • Training requirements for external support staff/contractors.	Training procedures in place and implemented.
11.	Personal hygiene	**Site related aspects:** 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.	**Site related aspects:** 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.

Reference number	Key quality element	Actions for implementation	Milestones
		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. **<u>QMS related aspects:</u>** 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 smoking material and personal medicines in production, quality control areas and warehouse areas • Training programs on personal hygiene	Adequate premises, equipment and technical measures in place ensuring containment of sensitizing/hazard-ous products and prevention of cross-contamination of materials and products due to personnel flow and cleaning of garments. **<u>QMS related aspects:</u>** Documented procedures ensuring GMP-conform personal hygiene in place and implemented.
12.	Premises**	**<u>Site related aspects:</u>** Define scope of premises by taking into account: • Environment in which the premises are built	**<u>Site related aspects:</u>** Scope of the premises defined.

Reference number	Key quality element	Actions for implementation	Milestones
		• 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 generally includes the following areas: • Warehousing including receipt and dispatch areas • Cleanrooms for sampling, dispensing and processing • Clean support areas (such as washing, movements and staging) • Packaging areas • Quality control laboratory • Process ancillary areas and equipment • Utilities The design of the premises should • Ensure logical flow of materials and personnel • Minimize the risk of errors and mix-ups • Permit effective cleaning • Prevent accumulation of dirt and dust • Provide suitable technical controls to prevent contamination and cross-contamination • Provide containment measures adequate for the operations and materials/products handled • Define suitable construction materials • Provide suitable environment for all operations taking place at site • Provide segregation of manufacturing operations performed at site • Permit effective maintenance • Permit adequate space for operations taking place • Prevent access of unauthorized personnel from entering site	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.

Reference number	Key quality element	Actions for implementation	Milestones

		• 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 control and warehousing areas
		  ○ Separation of maintenance workshops from production areas
		  ○ Separation of areas for secondary and subsequent packaging operations from cleanroom areas
		• Allow for effective pest control
		• Protect materials and products during receiving and dispatch procedures from weather and pest intrusion
		• Ensure separation of receiving and dispatch areas
		• Provide storage areas of sufficient capacity, adequate environment and security for the various categories of materials and products with proper separation and segregation
		• Provide utilities required and suitable space for generation and distribution
		• Provide back-up power to run essential operations in the event of power failures
		• Provide a suitable drainage system which has hygienic design and is able to prevent back-flow
		• Provide dedicated, self-contained areas in case sensitizing/hazardous products are manufactured
		• Provide segregated areas in case medicinal and non-medicinal products are manufactured
		• Provide separation of warehouses for raw material, packaging materials and finished goods from production areas
		• Provide Emergency installations (eye wash, emergency showers, firefighting equipment, etc.)
		
		Establishment of suitable contractors* and support staff for construction of site.
		
		Construction of premises complying with the design specifications.
			Suitable contractors and support staff identified and contracted.
			
			Premises complying with predefined specifications in place. Facility, as constructed, is conforming to

Reference number	Key quality element	Actions for implementation	Milestones
			original design drawings.
		QMS related aspects:	**QMS related aspects:**
		Development and implementation of a documentation system containing procedures, protocols, reports and records for qualification, maintenance and cleaning, sanitization of premises.	Documentation system for qualification, maintenance, cleaning and sanitization of premises in place and implemented.
		Development and implementation of a program for pest control outlining procedures and specifications for pest control, locations, frequency, the need and qualifications for contractors* including agreements.	Documented program for pest control including procedures for contractors in place and implemented.
		Development of a system defining the room status (e.g. clean, in operation, awaiting cleaning, under maintenance) within operational sections.	Documented system for defining room status in place and implemented.

13.	Equipment	**Site related aspects:**
		
		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.
		
		Definition of specifications, design and location of equipment to assure suitability of the equipment for its intended purpose taking into consideration factors such as:
		• Operational environment
		• Containment requirements
		• Material requirements, esp. for product contact areas, including
		  ○ Type of construction materials ensuring that they are not reactive, additive, absorptive or adsorptive
		  ○ Requirements on surface finishes/roughness
		• Cleanability/sterilization requirements
		• Prevention of (cross-) contamination
		• Maintenance which should have as little impact on clean room production processes as possible (e.g. by “through the wall” installations)
		• Ease of change-over
			Site related aspects:
			
			Equipment needs identified.
			
			Design specifications and layout/drawings of equipment and support systems available.

Reference number	Key quality element	Actions for implementation	Milestones
		• 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 equipment • Appropriate equipment number and capacity of equipment taking into consideration change-over and process cycle times • Suitability of dimensions and weight of equipment for its intended location of use • Controls and 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.	Suitable supplier(s) identified and contracts available.
		Installation/Commissioning of equipment complying with the design specifications.	Equipment complying with predefined specifications and design in place. As-built equipment conforms to original design drawings.
		QMS related aspects:	**QMS related aspects:**
		Development and implementation of a system containing documented procedures, protocols, reports and records for calibration, qualification, maintenance and cleaning, sanitization for each equipment.	System containing documented procedures, protocols, reports and records for calibration, qualification, maintenance and cleaning, sanitization for each equipment in place and implemented.
		Development and implementation of documented procedures for operation of equipment including records/logbooks.	Documented procedures for operation of equipment

Reference number	Key quality element	Actions for implementation	Milestones
			including records/logbooks in place and implemented.
		Development of a system defining the equipment status (e.g. clean, in operation, awaiting cleaning, under maintenance) within operational sections.	Documented system for defining equipment status in place and implemented.
		Development and implementation of documented procedures for handling of defect equipment and support systems.	Documented procedures for handling of defect equipment and support systems in place and implemented.
14.	Materials	**Site related aspects:** 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 to avoid any alteration of material and product during storage. The design has to ensure segregation of receiving and dispatch areas, that during receipt and dispatch materials and goods are protected from weather and that an effective pest control can be implemented. Access to storage, esp. to storage of labels, printed packaging materials and controlled substances, production and quality control areas has to be restricted to authorized personnel only. Based on the product classes manufactured, the manufacturing activities and the production capacity of	**Site related aspects:** Design specifications and layout for areas for storage, sampling, dispensing and material transport are in place. Areas complying with original specifications and design.

Reference number	Key quality element	Actions for implementation	Milestones
		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. **QMS related aspects:** Development and implementation of documented systems and procedures for receipt, handling, sampling, inspecting, release, rejection, dispensing, distribution and destruction of materials, labels, intermediates and finished products and defining authorized personnel performing these operations including: • Development and implementation of procedures ensuring that only materials of quality adequate for their intended use are purchased, received and handled • Definition of transportation and storage requirements for materials and products handled • Definition and implementation of procedures to ensure transportation and storage of materials and products in suitable environments with restriction of access where necessary • Definition and implementation of procedures for sampling, identity and integrity check of incoming consignments • Definition and implementation of procedures for labelling, storage and handling of materials, labels, intermediates and products according to their status, effectively preventing any mix-ups of materials with different status, and clearly defining authorized personnel for access and status change • Development and implementation of a system for unique identification of materials and products including identification code/batch numbers, sampling status, storage location and number of containers • Definition and implementation of procedures for stock rotation (e.g. first-expiry-first-out) and expiry control • Definition and implementation of procedures for regular stock reconciliation comparing actual versus recorded stocks • Definition and implementation of procedures for issuing and reconciliation of materials and products • Definition and implementation of procedures for dispensing of materials and handling of dispensed materials	**QMS related aspects:** Documented systems for receipt, handling, sampling, release, rejection, dispensing, distribution and destruction of materials, labels, intermediates and finished products in place and implemented.

Reference number	Key quality element	Actions for implementation	Milestones
		• 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	
15.	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 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,	Comprehensive documentation system in place and implemented.

Reference number	Key quality element	Actions for implementation	Milestones
		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	
16.	Good practices in production	**Site related aspects:** (Covered under "site related aspects" of key quality element 12: Premises). **QMS related aspects:** Development of a system to identify and classify substances handled regarding their potency and hazardous or sensitizing potential, and the derivation of containment requirements based on the classification done. 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. Development and implementation of procedures and records for all production related activities including in-process and environmental controls, line clearance and reconciliation procedures.	**Site related aspects:** (Covered under "site related aspects" of key quality element 12: Premises). **QMS related aspects:** System to identify and classify substances handled regarding their potency and hazardous or sensitizing potential, and the derivation of containment requirements based on the classification in place and implemented. Organizational procedures to avoid contamination and cross-contamination, and ensuring containment to the extent required is in place and implemented. Procedures and records for all production related activities including in-process and environmental controls, line

Reference number	Key quality element	Actions for implementation	Milestones
			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.
17.	Good Practices in Quality Control	**<u>Site related aspects:</u>** 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	**<u>Site related aspects:</u>** Analytical activities defined. Design specifications and layout for premises and equipment are suitable for performance of quality control activities.

Reference number	Key quality element	Actions for implementation	Milestones
		• Restriction of access to laboratory and its storage areas • Adequate space, environment and equipment to prevent mix-ups and (cross-)contaminations during inspection, testing of materials and 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 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 with 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.

Reference number	Key quality element	Actions for implementation	Milestones
		QMS related aspects:	**QMS related aspects:**
		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

Reference number	Key quality element	Actions for implementation	Milestones
			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 reagents and culture media, procedures for standardization and suitability testing where appropriate.	Procedures, records and logs for handling of reagents/solvents, culture media including required quality, identification of suppliers, receipt,

Reference number	Key quality element	Actions for implementation	Milestones
			identification/labelling, storage, expiration dating, issuance, use, master formulae for preparations of reagents and culture media, procedures for standardization and suitability testing where appropriate in place and implemented.
		Development and implementation of documented procedures, records and logs for handling of chemical reference standards including quality, source, procurement, receipt, labelling, storage, issuance, use, duration of use and lot number control.	Documented procedures, records and logs for handling of chemical reference standards in place and implemented.
		Development and implementation of documented procedures for preparation and handling of chemical in-house reference and working standards including details on reference material, preparation/standardization, retesting and re-standardization, labelling, storage, issuance, use, duration of use.	Documented procedures, records and logs for handling of chemical in-house reference and working standards in place and implemented.
		Development and implementation of procedures for handling of out of specification results (OOS) and out of trend results (OOT) addressing a phased approach consisting of initial laboratory investigations followed by full scale investigations as well as hypothesis testing, number and justification for retesting and resampling.	Procedures for out of specification results (OOS) and out of trend results (OOT) in place and implemented.
		Development and implementation of documents defining specifications and testing procedures for all raw materials, packaging materials, intermediates, bulk and finished products.	Documents defining specifications and testing procedures for all raw materials, packaging materials, intermediates, bulk and finished products in place and implemented.
		Development and implementation of programs for stability testing in line with WHO/ICH requirements.	Stability programs in place and implemented in line

Reference number	Key quality element	Actions for implementation	Milestones
			with WHO/ICH requirements.
		Development and implementation of a system for drawing, handling storage and inspection of retention samples.	System for drawing, handling, storage and inspection of retention samples in place and implemented.
		Definition and implementation of appropriate garment and safety procedures for protection of operator and environment and to avoid any contamination of samples.	Appropriate garment and safety procedures in place and implemented.
		Development and implementation of procedures for waste handling.	Procedures for waste handling in place and implemented.

* 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.

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