KENYA GMP ROADMAP

A Stepwise Approach for the Pharmaceutical Industry to Attain WHO GMP Standards

UNIDO

UNITED NATIONS
INDUSTRIAL DEVELOPMENT ORGANIZATION

REPUBLIC OF KENYA

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A Stepwise Approach for the Pharmaceutical Industry
to Attain WHO GMP Standards

Global UNIDO Project:
Strengthening the local production of
essential medicines in developing countries
through advisory and capacity building support

In collaboration with
Ministry of Industrialization and Enterprise Development
Ministry of Health
Pharmacy and Poisons Board
National Quality Control Laboratory
Federation of Kenya Pharmaceutical Manufacturers

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REPUBLIC OF KENYA

This document was prepared by UNIDO consultants Kay Weyer, Martin Nicholson and Wilberforce Wanyanga, and Alastair West, Senior Technical Advisor, under the supervision of Juergen Reinhardt, Project Manager. The Kenya GMP Roadmap was developed in conjunction with, and incorporating input and feedback from, key stakeholders in the Kenyan pharmaceutical sector including the Ministry of Industrialization and Enterprise Development, Ministry of Health, the Pharmacy and Poisons Board and the National Quality Control Laboratory, the Federation of Kenya Pharmaceutical Manufacturers, and other Kenyan pharmaceutical manufacturers.

FOREWORD FROM THE CABINET SECRETARY OF THE MINISTRY OF INDUSTRIALIZATION AND ENTERPRISE DEVELOPMENT

The manufacturing sector, which the Ministry of Industrialization and Enterprise Development (MOIED) supports, has a key role in the implementation of Kenya Vision 2030, which is the country's socio-economic development agenda for creating jobs, generating wealth, and attracting both local and foreign direct investment (FDI). The mandate of the Ministry of Industrialization and Enterprise Development (MOIED) in Kenya includes the development of Industrialization Policy, Kenya Property Rights Policy, Private Sector Development Strategy, Standards Development and Buy Kenya policy among others.

In carrying out its mandate, the Ministry developed the Sessional Paper No. 9 of 2012 of the National Industrialization Policy Framework for Kenya 2012–2030, whose theme is "Transforming Kenya into a globally competitive regional industrial hub". This policy, amongst others, also gives cognizance to the pharmaceutical sector as being vital to the industrial development of the country. In addition, the Ministry launched the Kenya Industrialization Roadmap in 2013 that seeks to increase the contribution of manufacturing base to GDP from 11 % of 20% in the medium term. The Ministry, on behalf of the Government of Kenya, is the focal point for all United Nations Industrial Development Organization (UNIDO) activities in Kenya.

In recognition of the important role played by the pharmaceutical industry, and especially as part of the Post-2015 Development Agenda, UNIDO worked with key local stakeholders including the Federation of Kenya Pharmaceutical Manufacturers and the Pharmacy and Poisons Board to develop the 'Pharmaceutical Sector Profile: Kenya' document, which was published in 2010. This was followed by the 'Kenya Pharmaceutical Sector Development Strategy' (KPSDS) in 2012. The KPSDS identified seven strategic components and Good Manufacturing Practice (GMP) was recognized as being central to the stated ambition for the sector.

The stakeholders in the sector including the Ministry of Industrialization and Enterprise Development, Ministry of Health, Federation of Kenya Pharmaceutical Manufacturers, Pharmacy and Poisons Board, National Quality Control Laboratory among others then continued to collaborate with UNIDO to start in earnest the development of a five year plan which constituted the Kenya GMP Roadmap for attaining WHO GMP. This roadmap is the first strategic component of the KPSDS.

The Kenya GMP Roadmap document covers fundamental principles in line with World Health Organization (WHO) GMP, which is the overarching consideration for developing such a plan. It also contains the baseline assessment of existing manufacturing practices in the Kenyan pharmaceutical industry including assessment approach, development of tools for assessment, key quality elements, focus areas during assessment and the assessment schedule, rating of observations, tools for evaluation of assessment results, selection of local companies for assessment, assessment results and evaluation.

The assessment results and evaluation were then used to develop a GMP roadmap delineating a two-phased approach: phase I is a period not longer than 3 years which will mainly focus on the establishment of WHO GMP compliant manufacturing sites and key Quality Management System GMP aspects, followed by Phase II which covers a period not longer than 2 years and which will focus on the establishment of a comprehensive Quality Management System. The document also encompasses the implementation plan for the roadmap. The roadmap underwent various stages of consultative and participatory engagement with key stakeholders prior to its finalization as the Kenya GMP Roadmap document.

It is envisaged that at the end of the implementation of this plan the local pharmaceutical manufacturing industry will be able to meet local demands as well as increase its presence on the international market, provide more employment and contribute to availability of foreign exchange through reduced imports. Importantly, the Kenyan population will be healthier as a result of accessing high quality medicines produced according to WHO standards of production.

I wish to thank all the stakeholders who made it possible for the development of the Kenya GMP Roadmap including Senior Officials from MOIED, Ministry of Health, UNIDO, Federation of Kenya Pharmaceutical Manufacturers, Pharmacy and Poisons Board, National Quality Control Laboratory, and the Kenya Medical Supplies Agency among others.

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FOREWORD FROM THE CABINET SECRETARY OF THE MINISTRY OF HEALTH

The Kenya Health Policy 2012-30 is one of the components for delivery of the Vision 2030's social pillar, given the key role it plays in maintaining a healthy and skilled workforce necessary to drive the economy. To realize this ambitious goal, the health sector defined priority reforms as well as flagship projects and programs, including restructuring of the sector's leadership and governance mechanisms; improving procurement and availability of essential medicines and medical supplies; modernizing health information systems; accelerating health facility infrastructure development to improve access; improving human resource for health development; developing equitable financing mechanisms, and establishment of social health insurance. This policy aims to implement the priority health reforms to ensure a healthy workforce capable of contributing towards the country's development agenda.

The Kenya National Pharmaceutical Policy (KNPP) contained in the Sessional Paper No. 4 of 2012 sets out the framework for the development of the pharmaceutical sector vide the policy statement. The UNIDO global project on strengthening local pharmaceutical production, which began in 2009, provides such a platform to realize this goal. In this regard, the Government provides the necessary enabling policy environment. This will enhance the overall policy goal, that is, universal access to quality essential medicines, essential health technologies and pharmaceutical services in Kenya. The overall objective of the KNPP is to ensure equitable access to essential medicines in Kenya through, amongst others, encouraging local manufacture of essential medicines for self-sufficiency in the domestic market and to promote growth in pharmaceutical exports.

There are over 30 local pharmaceutical manufacturers now engaged in the formulation and packaging of pharmaceutical products for human and veterinary use, which offers great potential for Kenya to attain self-sufficiency in essential medicines and to serve the export market, while creating much needed employment. Since Kenya subscribes to WHO GMP, it will require strong regulatory oversight and enforcement. A well-regulated pharmaceutical sector fosters consumer confidence in the medicines originating from, and those circulating in, the Kenyan market.

The KNPP takes into consideration that pharmaceutical sector enterprise development should be supported while safeguarding public health, and the regional integration within the EAC and COMESA provides market opportunities. Globalization is a key feature of the pharmaceutical sector, and it calls for harmonization of standards and reciprocity in market control and regulation, and coherence in policy.

The Kenya GMP Roadmap sets out an ambitious five year plan that will bring pharmaceutical manufacturers up to WHO GMP standards in a step-by-step individualized improvement program. It envisages a plan that matches short-term and long-term goals with specific technology solutions to help meet those goals. This plan has undergone various stages of consultative and participatory engagement driven by both the government and the local pharmaceutical industry with an open window to all manufacturers (represented through MOH, MOIED, PPB, NQCL and FKPM). It is an all inclusive program requiring the need for continuous availability of expertise at facility and national level. It will also require the activation of other strategic components envisioned in the KPSDS.

The justification of approach is founded on the basis arising from the assessment of the industry, which identified that:

- A few leading companies meet WHO GMP standards
- Some companies have endeavoured to upgrade within the limitations that they face, albeit ahead of the onset of the roadmap
- Some manufacturers are operating well below GMP standards and need technical assistance in areas including GMP gap analysis, facility design, corporate culture, personnel, processes, validation, stability studies, HVAC, water treatment, QC functions, QA functions and so on.

The Ministry of Health will continue to collaborate with its counterpart, the Ministry of Industrialization and Enterprise Development, and with UNIDO to ensure the key outcomes inter-alia, quality essential medicines are available, the manufacturers are WHO GMP compliant and the Pharmacy and Poisons Board is listed amongst the stringent pharmaceutical regulators on the African continent, through the implementation of the seven pillars of the Kenya Pharmaceutical Sector Development Strategy. Therefore the launch of the Kenya GMP Roadmap is in itself a major milestone in Kenya and indeed the region.

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ACRONYMS

CAPA	Corrective and Preventive Action
Ctd.	Continued
EAC	East African Community
EAC PMPOA	East African Community Regional Pharmaceutical Manufacturing Plan Of Action
FIFO	First In First Out
FEFO	First Expiry First Out
FKPM	Federation of Kenya Pharmaceutical Manufacturers
GMP	Good Manufacturing Practice
HR	Human Resources
HVAC	Heating Ventilation and Air Conditioning
KPSDS	Kenya Pharmaceutical Sector Development Strategy
MEAC	Ministry of East African Community
MOH	Ministry of Health
MOIED	Ministry of Industrialization and Enterprise Development
MS	Milestone
OOS	Out Of Specification
OOT	Out Of Trend
PMPA BP	Pharmaceutical Manufacturing Plan for Africa Business Plan
PPB	Pharmacy and Poisons Board
PPOA	Public Procurement Oversight Authority
Q	Quarter
QA	Quality Assurance
QC	Quality Control
QMS	Quality Management Systems
RA	Regulatory Authority
SC	Strategic Component (of KPSDS)
SOP	Standard Operating Procedure
TOR	Terms of Reference
UNIDO	United Nations Industrial Development Organization
WHO	World Health Organization
Y	Year

I. INTRODUCTION

This document presents a Good Manufacturing Practice (GMP) Roadmap for the Kenyan pharmaceutical industry as a guide to relevant policy makers, regulators and other stakeholders as well as the manufacturers themselves. It has been developed following identification of the need for a plan to inform relevant parties as to how to attain WHO GMP standards of pharmaceutical production. This plan encompasses a practical, stepwise process that can be implemented in Kenya over a defined period of time. The need for a Kenya GMP roadmap was established through UNIDO's work with multiple stakeholders in Kenya, in an inclusive process.

The project has completed a number of phases. Having started in 2009, during the first phase an initial Kenya Pharmaceutical Profile was produced. This highlighted that the sector had a strong pharmaceutical manufacturing foundation, albeit with varying levels of compliance to internationally acceptable GMP standards. It further indicated that through the development of the sector, the country's overreliance on imported pharmaceuticals could be addressed and that it could contribute to tackling the scourge of substandard medicines.

Based on initial findings from the Kenya Pharmaceutical Profile and through a multi stakeholder consultative process, during the second phase the Kenya Pharmaceutical Sector Development Strategy (KPSDS) was developed. This was endorsed at a multi stakeholder meeting on August 27, 2011 in Nairobi. The KPSDS sets out an ambition for the industry to achieve WHO GMP standards of production for the benefit of all stakeholders. For example, it would improve access to medicines (both availability and quality) for patients, and would contribute to the economic growth of the country through a reduced reliance on imports and through increasing exports of pharmaceuticals. This latter benefit offers significant commercial opportunities for the Kenyan pharmaceutical industry, based on the reputation of Kenya as being a local centre of excellence in pharmaceutical production.

The KPSDS identified seven strategic components. These need to be addressed for international standards of production, specifically WHO GMP standards, to be universally achieved and for the industry to be economically sustainable and therefore able to contribute to public health and economic development of the country. These strategic components are shown in the following table.

Table 1: Seven Strategic Components in KPSDS

Strategic Component	***Aim***
1) Setting out a roadmap for industry to achieve GMP Standards	To achieve WHO GMP in a stepwise manner
2) Strengthening mechanisms for quality assurance of medicines in the distribution chain	To establish a national quality assurance system that will identify and remove from the market non compliant products, and enhance the pharmacovigilance activities
3) Strengthening Regulatory Capacity	To enhance regulatory oversight in tandem with industry growth and international trends
4) Accessing Required Financing for Investment in the Sector	To facilitate access to affordable finance
5) Devising Time-Limited Incentives for Industry	To assist the industry in remaining competitive whilst it is investing in quality infrastructure and products
6) Developing Necessary Human Resources	To enhance human capital with knowledge, skills, and competence, as required in the sector
7) Developing common support services for local pharmaceutical companies	To create a platform for pooling and sharing of technical resources

As can be seen in Table 1, establishing a GMP roadmap was identified as being central to the stated ambition for the sector and represents a key aspect of the third phase of the project, following on from the first two phases as outlined above.

Accordingly in the third quarter of 2012 field work to inform the development of the roadmap was conducted under the lead of a pharmaceutical manufacturing expert. This document describes the field work that was undertaken and how this was used to develop the roadmap. The remaining six strategic components within the KPSDS, which are also fundamental to successful development of the sector, will be further defined in the course of time.

The ambitious five year plan to strengthen and upgrade pharmaceutical manufacturers to WHO GMP standards has been developed in close collaboration with local stakeholders. It has undergone various stages of consultative and participatory engagement involving the Government and the local manufacturing industry, as represented through the Ministry of Health (MOH), Ministry of Industrialization and Enterprise Development (MOIED), Pharmacy and Poisons Board (PPB), National Quality Control Laboratory (NQCL), the Federation of Kenya Pharmaceutical Manufacturers (FKPM), as well as a variety of other government agencies and individual manufacturers including non-FKPM members.

It was acknowledged that for a GMP roadmap to be implemented, key stakeholders including the industry and the regulator needed to have a reasonable understanding of the requirements for WHO GMP standards, as a common ground. This would allow the stakeholders to be cognizant of the implications and be able to participate in the consultative process that was proposed to refine the initial draft of the roadmap into a proposal that would be

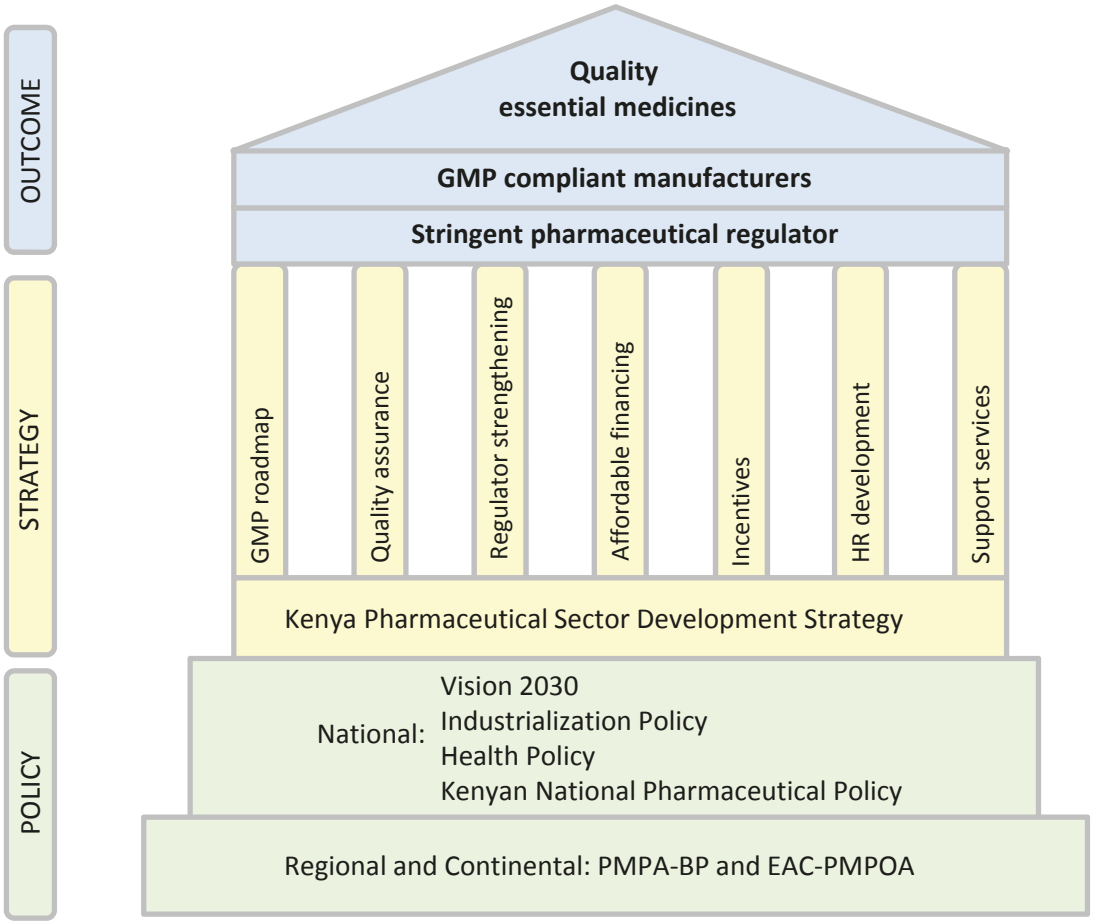
agreed to by all parties. Hence a number of GMP training modules and a number of GMP workshops for industry representatives (both technical and managerial) as well as policy makers and regulators, were carried out by a pharmaceutical manufacturing expert in 2013 and 2014.

The Kenya GMP Roadmap is the first strategic component in a holistic approach for the development of the pharmaceutical manufacturing industry. The need identified in Kenya is well anchored in a number of continental and regional policy documents. The African Union Commission's Business Plan for the Pharmaceutical Manufacturing Plan for Africa [1](PMPA BP) analyses the constraints faced by the industry on the continent and recommends a package of solutions. It is stated in the Forewords that there is a dire need for promoting sustainable development of the sector to improve access to quality affordable medicines. The notion of a GMP roadmap is included in this document as well as the suggestion that the technical roadmap and risk assessment of companies be linked with an assessment of the potential risk to health related to sub-GMP manufacture of specific products. This dimension is not specifically covered in this document which focuses on the details of GMP, however the PPB and other stakeholders may consider combining such a product dimension to the initiative as a way to mitigate risk to public health during the transition to WHO GMP standards. The East African Community Regional Pharmaceutical Manufacturing Plan of Action 2012-2016 (EAC-PMPOA) is a framework to guide the EAC towards developing an efficient and effective regional pharmaceutical manufacturing sector that can supply markets with efficacious quality medicines[2].

On the national level Vision 2030 details the long term national development agenda aiming to transform Kenya into a middle income country by 2030. This is supported by the National Industrialization Policy Framework for Kenya 2012-2030[3] which focuses on transforming Kenya into a globally competitive regional industrial hub. In more specific terms, the Kenya Health Policy 2012-2030[4] aims at implementing the Kenya Constitution which sets out the requirement for "attaining the highest possible standard of health in a manner responsive to the needs of the population". The National Pharmaceutical Policy[5] on reforming the pharmaceutical sector to ensure equitable access to essential health products and technologies is emphatic on the need for developing local production and states that "the Government will promote self-sufficiency in essential medicines production and growth in pharmaceutical exports".

1 Pharmaceutical Manufacturing Plan for Africa: Business Plan 2012
2 East African Community Regional Pharmaceutical Manufacturing Plan of Action: 2012 - 2016
3 Sessional Paper No 9 of 2012on The National Industrialization Policy Framework for Kenya 2012 – 2030
4 Kenya Health Policy 2012 - 2030
5 Sessional Paper No 4 of 2012 on National Pharmaceutical Policy July 2012

Figure 1: Policies and strategies supporting the delivery of quality essential medicines



The main part of this document describes the process of developing the roadmap including the tools that were designed and the rationale behind the structuring of what is proposed. The specifics of the roadmap, the details of the tools that were developed and the provisional implementation plan are contained in the document's annexes and appendices.

II. THE KENYA GMP ROADMAP

1. Fundamental principles of GMP and the overarching consideration for developing a roadmap

Adherence to Good Manufacturing Practice (GMP) is essential to ensure that quality of medicinal products is assured consistently and that the products are safe and efficacious. But due to the lack of financial, technical and human resource capacities pharmaceutical manufacturers in Kenya are often overwhelmed by the vast array of GMP requirements causing companies not to operate in line with internationally acceptable GMP standards. The international GMP standard referred to in this context is the GMP standard as outlined by the World Health Organization (WHO)[6] with its unified standards which receive wide international acceptance.

A roadmap delineating a phased approach to WHO GMP compliance tailored to the specific situation in Kenya needed to be developed setting out requirements and milestones for pharmaceutical manufacturers to be achieved on their progress from the current level of GMP compliance to full WHO GMP compliance over a specified period of time.

In order to establish the baseline of the current manufacturing practices across the range of companies in Kenya, assessments of Kenyan pharmaceutical manufacturers were conducted in order to gauge their level of compliance to Good Manufacturing Practice (GMP). Based on the results gathered during these assessments, a phased, risk-based approach to compliance with WHO GMP has been developed. In this context a tool for risk categorisation of companies, based on their compliance to WHO GMP, has also been developed.

The resulting GMP roadmap, tailored for the pharmaceutical industry in Kenya, will be used as a stepwise tool to guide companies and regulatory authorities on the path towards WHO GMP. Companies that are currently operating can use the roadmap together with the risk assessment in order to perform a gap analysis between their current GMP compliance and WHO GMP requirements and to follow a stepwise approach towards WHO GMP compliance. New start-up companies can use this roadmap to assure that all necessary elements and systems are taken into consideration and to assure that they are in place before the actual launch of the company. The roadmap will enable the regulatory authority to review licensing criteria for new and existing facilities in order to ensure that licensing criteria are in line with WHO GMP requirements.

In addition to the Kenya GMP Roadmap, an implementation plan has been developed in collaboration with stakeholders. This embraces the multiple facets required for successful implementation of the roadmap towards compliance with WHO GMP requirements.

6 The GMP standard referred to in this document is the standard as outlined by the WHO in "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" and subsequently updated through the WHO Technical Report Series (TRS) especially TRS 961, Annex 3.

2. Objectives

Given that a pathway towards compliance with WHO GMP tailored to the specific situation in Kenya had to be developed, the objectives of the conducted work were:

- Performance of a baseline assessment of existing manufacturing practices in the Kenyan pharmaceutical industry based on company assessments, in order to evaluate the level of compliance with WHO GMP across the range of pharmaceutical companies in Kenya, and also to identify the main technical challenges faced by these pharmaceutical manufacturers.

- Development of a GMP roadmap reflecting outcomes of the baseline assessment. In order to develop a sound scientific and achievable approach towards implementation of WHO GMP, the Kenya GMP Roadmap needed to delineate a risk-based, phased approach towards compliance with WHO GMP.

- Development of an implementation plan, in collaboration with stakeholders, to facilitate successful implementation of the GMP roadmap.

3. Scope

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

- **Non – sterile dosage forms** that are solid, liquid or semi-solid formulations not intended to be used for injection, infusion, implantation, application to the eye, or on large open wounds or severely injured skin and hence do not have to fulfil requirements for the manufacture of sterile dosage forms and do not need to comply with the test for sterility as described in the pharmacopoeias.

- **Medicinal products containing small molecular entities** that are active substances with a molecular weight of not more than 800 g/mol. To date most active substances are small molecular entities.

4. Baseline assessment of existing manufacturing practices in the Kenyan pharmaceutical industry

As a starting point for development of the Kenya GMP Roadmap, the baseline of the current manufacturing practices over a representative cross-section of companies in Kenya needed to be established, and main technical challenges needed to be identified. Therefore, assessments of the level of compliance of pharmaceutical manufacturers in Kenya to Good Manufacturing Practice (GMP), as outlined by the World Health Organization (WHO), were performed.

4.1 Approach

The following approach was used in order to perform a baseline assessment of existing manufacturing practices in the Kenyan pharmaceutical industry:

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

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

The focus of the baseline assessment was on companies with differing levels of compliance to WHO GMP, but which had not yet achieved full compliance. This was designed to reflect the compliance range found within Kenyan pharmaceutical manufacturers as a whole. Several pharmaceutical companies had to be assessed using unified procedures, and the results gathered had to be evaluated using unified criteria. Therefore, before the baseline assessment was conducted, unified tools had to be developed which could then be applied to each pharmaceutical manufacturer participating in the baseline assessment in order to perform a transparent assessment of the Kenyan companies. So, for all companies assessed, the same criteria were used. These tools, developed by a pharmaceutical manufacturing expert, were:

- Definition of a GMP reference standard for assessment of companies
- Definition of key elements and focus areas during assessments
- Preparation of an assessment schedule to be applied for all companies
- Definition of rating of observations
- Definition of tools for evaluation of assessment results

4.2.1 GMP reference standard for assessment of companies

The internationally recognized GMP standard used as reference for the assessment of pharmaceutical manufacturers in Kenya was the GMP standard as outlined by the World Health Organization (WHO) in the document "Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2, 2nd updated edition. Good manufacturing practices and inspection. World Health Organization, Geneva, 2007" as subsequently updated through the WHO Technical Report Series (TRS) especially TRS 961, Annex 3.

WHO GMP was selected as the GMP reference standard. This 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 Kenya strive to achieve compliance with WHO GMP as part of the requirements for having their products prequalified by WHO.

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

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

1. Quality assurance
2. Utilities impacting Good Manufacturing Practice (GMP)
3. Sanitation and hygiene
4. Qualification and validation
5. Complaints
6. Product recalls
7. Contract production and analysis
8. Self-inspection and quality audits
9. Personnel
10. Training
11. Personal hygiene
12. Premises
13. Equipment
14. Materials
15. Documentation
16. Good practices in production
17. Good practices in quality control

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

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

4.2.3 Rating of observations

Observed deficiencies were rated based on the compilation of EU community procedures on inspections and exchange of information (London, 25 May 2012, EMA/INS/

GMP/321252/2012 Rev 14). The assessments were performed during November and December, 2012, and the deficiencies were classified as follows:

Critical Deficiency:

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

Major Deficiency:

A non-critical deficiency,
which has produced or may produce a product, which does not comply with its marketing authorisation;
or
which indicates a major deviation from Good Manufacturing Practice;
or
which indicates a major deviation from the terms of the manufacturing authorisation;
or
which indicates a failure to carry out satisfactory procedures for release of batches or a failure of the Authorized Person to fulfil his/her legal duties;
or
a combination of several "other" deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such.

Other Deficiency:

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

4.2.4 Tools for evaluation of assessment results

In order to evaluate the level of compliance of Kenyan pharmaceutical manufacturers with WHO GMP and to identify main technical challenges across the range of pharmaceutical companies in Kenya, two tools have been developed:

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

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

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

A tool needed to be developed that allows for comparison of compliance of companies with WHO GMP and that identifies those key quality elements to which highest and lowest com-

pliance were observed. The usage of the plain ratings of individual observations made during the assessment of individual companies would not have been suitable due to the variety of individual observations. Therefore, based on the rating of observations made during the assessment of the companies, a rating of the compliance of key quality elements with WHO GMP was derived. A rating key was developed which made it possible that observations related to a specific key quality element were rated as a whole reflecting the 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 on areas related to this specific key quality element.

- Improve: Compliance of a key quality element with WHO GMP was rated "Requires improvement" (short: "improve") if only few "major" deficiencies (< 5) were observed on areas related to this specific key quality element.

- Inadequate: Compliance of a key quality element with WHO GMP was rated "Inadequate" if at least one "critical" and/or a considerable number (> 5) of "major" deficiencies were observed on areas related to this specific key quality element or the entire quality element not available at a company.

This rating key made it possible to compare company performances and to identify those key quality elements to which highest and lowest compliance were observed. Hence, main technical challenges for compliance could be identified. The rating key is a useful tool to evaluate particular weaknesses in compliance that pharmaceutical manufacturers within a country are facing.

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

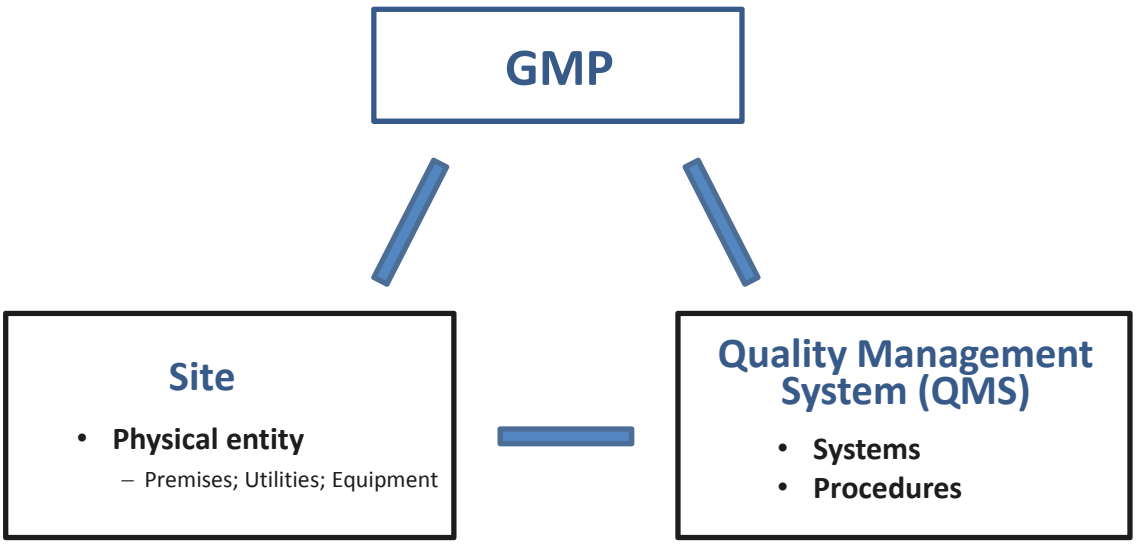
Tool 2: Categorization of companies based on their compliance with WHO GMP

GMP compliance encompasses the implementation and adherence to a vast array of requirements. Depending on the financial, technical and human resource capacities available to pharmaceutical manufacturers, the adherence to GMP compliance varies significantly between pharmaceutical manufacturers in Kenya. This ranges from companies that are compliant with WHO GMP to companies that have multiple critical issues to address.

The significant range in adherence to GMP compliance by pharmaceutical manufacturers required the development of a tool for risk categorization in order to evaluate the compliance risk associated to the pharmaceutical manufacturers that were assessed.

GMP compliance can be understood as the result of compliant structural and compliant organizational measures. In this document the term "site" is used for the physical entity of mainly premises, utilities and equipment used for pharmaceutical manufacturing. The term "quality management system"(QMS) is applied to all documentation systems and procedures used by a company to ensure GMP compliance. The interconnection between site, QMS and GMP is illustrated in figure 2.

Figure 2: Interconnection between site, QMS and GMP



The classification uses a matrix to categorize companies based on the two risk-indicating factors for GMP compliance:

- Compliance of site with WHO GMP standards
- 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 score of "1", "2" or "3" was assigned to both site and quality management system to describe their compliance with WHO GMP, with a score of "3" representing a high compliance risk and a score of "1" representing a low compliance risk.

Table 2: Risk matrix for categorization of companies based on their GMP compliance

		Quality Management System (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 company

B: Existing approach towards pharmaceutical manufacturing not in line with WHO GMP but reduced risk with regards to production safety → medium risk company

C: Existing approach towards pharmaceutical manufacturing not in line with WHO GMP and high risk with regards to production safety → high risk company

A matrix, shown in Table 2 above, was provided for combining these two scores in order to generate an estimate of the compliance risk associated with a pharmaceutical manufacturer. The resulting risk ratings were "A", "B" and "C". A rating of "C" indicates high risk companies with non-compliance to WHO GMP, even causing a high risk to production safety. A rating of "A" indicates low-risk companies, where the existing approach towards pharmaceutical manufacturing is, in general, in line with WHO GMP requirements.

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

This risk categorization is a suitable tool for benchmarking GMP compliance of companies and can also be used in conjunction with tool 1 presented in 4.2.4. to monitor the companies' development towards full WHO GMP compliance.

4.3 Selection of companies for assessment

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

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

1. Pharmaceutical manufacturers having not yet achieved full compliance with WHO GMP
2. Pharmaceutical manufacturers representing different stages of development of companies in the private sector
3. Pharmaceutical manufacturers willing to participate in the assessment

An initial screening of companies to determine eligibility according to the above criteria was conducted using a questionnaire, which was distributed to all manufacturers including members of the Federation of Kenya Pharmaceutical Manufacturers (FKPM). After screening had confirmed eligibility of companies willing to participate in this project, company assessments were performed by a pharmaceutical manufacturing expert, in conjunction with the national pharmaceutical project coordinator, using the tools described in section 4.2.

4.4 Assessment results and evaluation

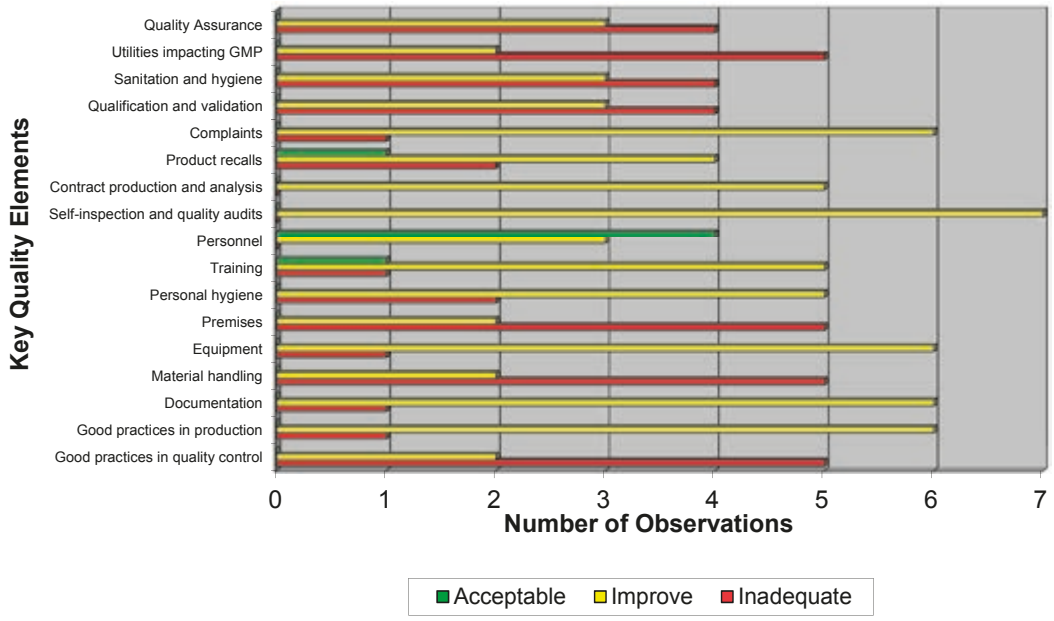
The company assessments were performed in 2012, using the criteria as described in section 4.3. During the assessments seven companies were reviewed regarding their compliance with WHO GMP. The results gathered during the assessments have been anonymized:

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

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

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

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



From the above results it can be seen that the compliance of the vast majority of the key quality elements with WHO GMP needed improvement or was inadequate. Although companies participating in the assessment were very interested in upgrading their GMP compliance, the number and severity of observations indicated that there were varying degrees of awareness of WHO GMP requirements within both the pharmaceutical industry, and the regulatory authority that had licensed the participating companies for manufacturing and hence had certified them for GMP compliance. This indicated a high need for training not only of pharmaceutical manufacturers but also of the regulatory authorities in order to properly understand WHO GMP requirements and in order to be able to evaluate the compliance of Kenyan companies with WHO GMP. Despite the high number of quality elements which were either rated "inadequate" or "improve", the scientific degrees held by company personnel was, for the majority of companies, adequate. This observation is reflected in the rating for the key quality element "Personnel". The discrepancy between the adequate scientific degrees of personnel and the limited knowledge of WHO GMP requirements potentially illustrates a general problem with existing educational systems and highlights a high need for review of academic and post-academic curricula, as well as the need for continuous training for staff working in both pharmaceutical companies and the regulatory authority.

Figure 3 reveals that the key quality elements with the least compliance with WHO GMP and hence with the highest numbers of the rating "inadequate" are:

- Utilities impacting GMP
- Premises
- Material handling
- Good practices in quality control

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

terial handling" results from observations regarding both constituents of GMP, namely site and QMS. The "inadequate" rating for the key element "Good practices in quality control" resulted mainly from observations regarding QMS.

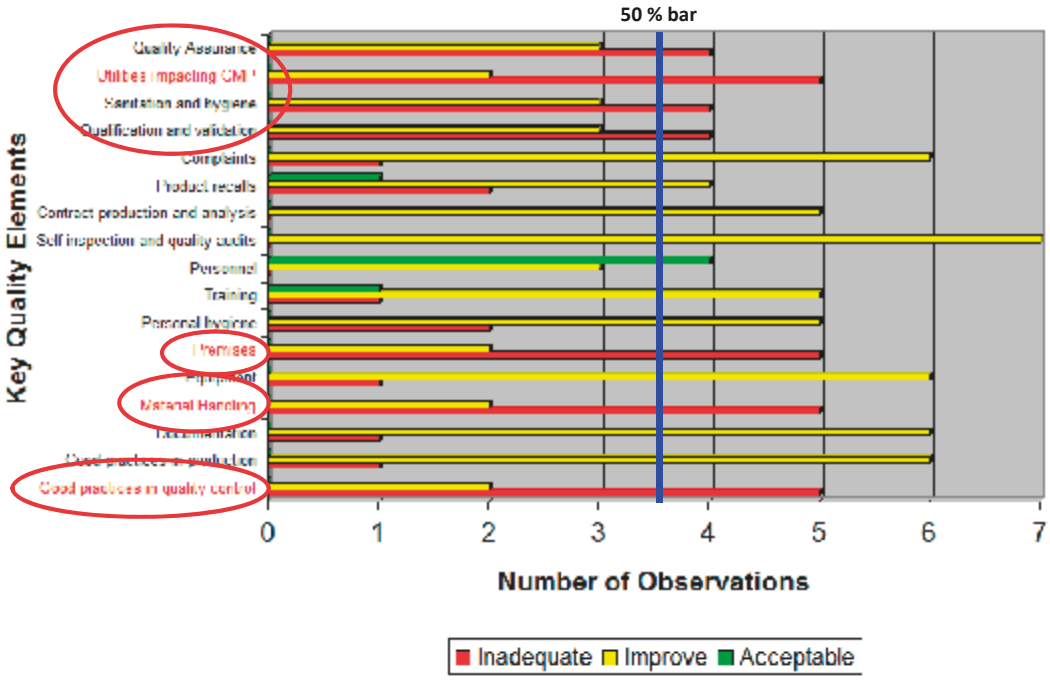
The high number of "inadequate" ratings of the key elements "Utilities impacting GMP" and "Premises" is directly related to the site, and the high number of "inadequate" ratings of the key element "Material handling" are caused by significant deficiencies in both components of GMP, namely site and QMS. These facts indicate that a main challenge for WHO GMP compliance in Kenya is the lack of GMP conforming sites. Consequently, there is a high need for the provision of guidance to manufacturers on site design requirements. Due to the high number of significant deficiencies related to site, and due to the fact that in general site related modifications are difficult and quite costly, it is clear that the roadmap towards WHO GMP requires a strong initial focus on improvement of site related GMP aspects.

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

- Quality assurance
- Sanitation and hygiene
- Qualification and validation

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

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



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

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

- Quality assurance
- Utilities impacting Good Manufacturing Practice (GMP)
- Sanitation and hygiene
- Qualification and validation
- Premises
- Material handling
- Good practices in quality control

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

Companies participating in the assessment have been risk categorized using tool 2 as described in section 4.2.4. The risk categorization was based on the WHO GMP compliance of two risk-indicating factors, namely:

- Compliance of site with WHO GMP standards
- Compliance of quality management systems with WHO GMP standards

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

Table 3: Results of company categorization, based on their compliance with WHO GMP

Company name	*Risk score Site*	*Risk score QMS*	*Overall GMP rating*
Company 1	2	1	B
Company 2	2	2	B
Company 3	3	2	C
Company 4	3	2	C
Company 5	3	2	C
Company 6	3	2	C
Company 7	3	3	C

The categorization shows that out of the seven companies assessed only two companies received an overall GMP rating of "B" (medium risk company) whereas the remaining companies got an overall GMP rating of "C" (high risk company). The risk scores for compliance of QMS with WHO GMP requirements ranged from "1" to "3", whilst the risk scores for compliance of site with WHO GMP requirements ranged from "2" to "3". This result verifies that the selection of companies was suitable for the assessment, as the selection criteria were designed to define only companies that have not yet achieved full compliance with WHO GMP (no company with an overall GMP rating of "A" was included in the assessment), and to provide a representation of the different stages of development of entities in the private sector (risk scores ranging from "1" to "3" could be observed).

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

Comparing the risk scores for site and QMS, it becomes clear that the risk scores for site are in general different from the risk scores for QMS, since the risk associated to site is usually higher than risk caused by QMS. The compliance risk regarding QMS was rated with a risk score of "2" for the majority of companies (5 out of 7 companies), meaning that QMS are implemented sporadically. One company achieved a risk score of "1" reflecting that a systematic approach towards a QMS in line with WHO GMP requirements was in place. Only one company had no QMS in place (risk score of "3"). Whereas 6 out of 7 companies attained a risk score for QMS of "2" or better, the majority of companies (5 out of 7 companies) received a site related risk score of "3" reflecting that the existing site is impairing production safety. Only two companies attained a site related risk score of "2" meaning that significant deficiencies from WHO GMP exist but that production safety is not impaired. The usually higher risk associated to site was, for almost all companies, the main reason for the downgrading of overall GMP compliance rating. The risk scores for site and QMS were the same for only two companies.

The result of the risk assessment - that the high compliance risk associated to site is a major reason for low compliance with WHO GMP - underlines the observation made after the compliance rating of the key quality elements, which showed that the highest number of "inadequate" ratings was mainly obtained for key quality elements that are directly or at least partly associated to site.

The fact that the high compliance risk for site was the main reason for lowering the overall GMP rating clearly indicates that strong guidance is needed regarding site related GMP aspects and design requirements. Based on the outcome of the company assessments, site related GMP aspects need to be one of the key aspects during design of the GMP roadmap. Nevertheless, it has to be pointed out in this context that although the compliance risks related to QMS were lower than the ones related to site, the presence of only sporadically implemented quality management systems or the absence of an entire QMS are serious deficiencies from WHO GMP and need urgent improvement in order to ensure quality, safety and efficacy of the manufactured products. Besides, it has to be taken into consideration that the construction of new, WHO GMP compliant sites or modification of existing manufacturing sites are time consuming and costly, whereas the urgently needed implementation of currently absent quality management systems or the correction of existing quality management systems in line with WHO GMP requirements can be done in a shorter timeframe and is generally less costly.

4.4.3 Conclusions drawn from the assessment

The following conclusions can be drawn from the assessment performed at pharmaceutical companies in Kenya:

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

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

5. Kenya GMP Roadmap towards WHO GMP

The Kenya GMP Roadmap document was developed after performing the baseline assessment of Kenyan pharmaceutical manufacturers in 2012, regarding their existing level of compliance to WHO GMP (as described in section 4 of this document), and through subsequent meetings during the course of 2013 with key stakeholders including representatives from industry and government (both policymakers and regulators).

The roadmap delineates a phased approach to WHO GMP compliance and sets out requirements and milestones for pharmaceutical manufacturers, to be achieved during the progression of these companies from their existing levels of GMP compliance up to full WHO GMP compliance over a specified period of time. In order to ensure that the roadmap presents an achievable and hence realistic pathway towards full WHO GMP compliance the approach to its development of this roadmap was:

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

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

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

The baseline assessment revealed not only that site related GMP aspects need to be priority points to be improved, but also that immediate measures are required in order to reduce risks caused by the quality management system (QMS). Therefore, the roadmap focuses first on the establishment of a WHO GMP compliant site and on those quality management systems that were identified as having the most significant deviations from WHO GMP.

Taking these results into account, the Kenya GMP Roadmap has been developed delineating a **two-phased approach**.

5.1 Phases

Phase I

During the initial phase the focus of the roadmap is on:

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

Although the key quality element "equipment" was not identified as showing serious deficiencies for the majority of companies it is within the first focus due to its impact on site and qualification.

Based on the key quality elements with the lowest compliance in Kenya the focus during phase I is on the following key quality elements:

- Quality assurance
- Utilities impacting Good Manufacturing Practice (GMP)
- Sanitation and hygiene
- Qualification and validation
- Premises
- Material handling
- Good practices in quality control
- Equipment (added in Phase I not due to severity of deficiencies but due to the focus on site)
- Any site related aspects of other key quality elements

Phase II

The main focus during the subsequent phase is on:

- Establishment of a comprehensive quality management system ensuring a systematic approach to WHO GMP.

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

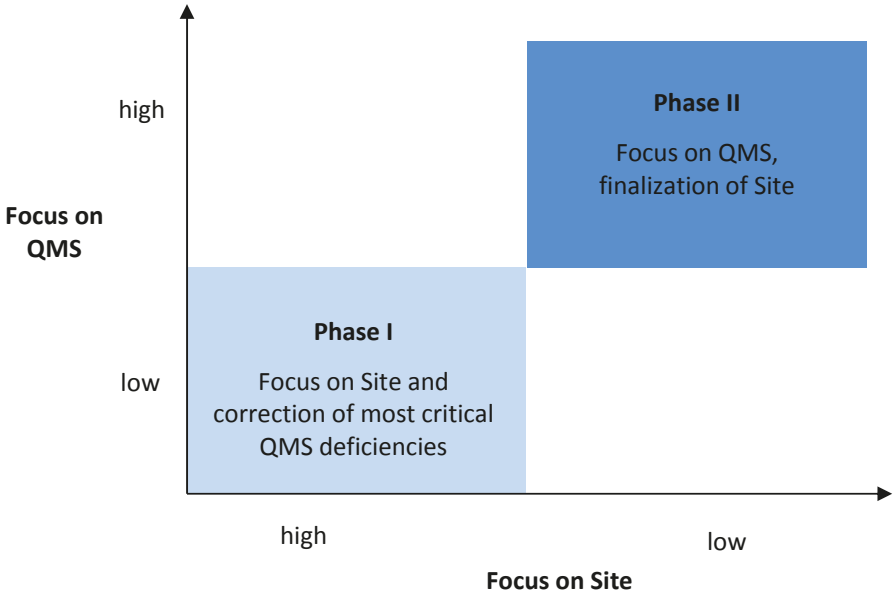
The focus during phase II will be on the following key quality elements:

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

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

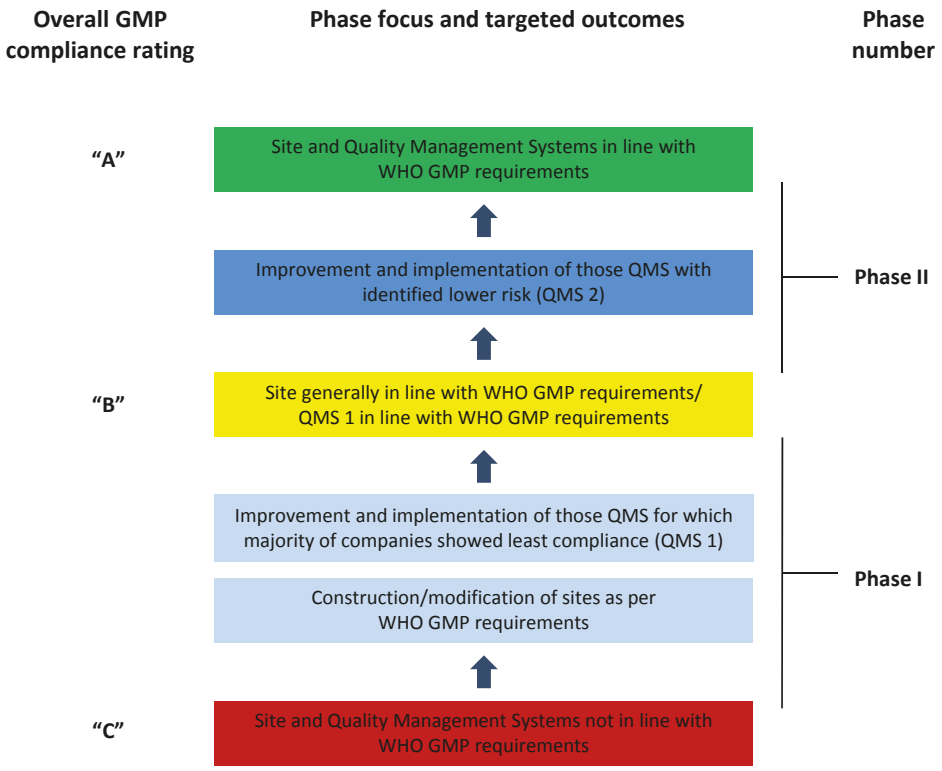
This phased approach will allow companies to make stepwise improvements from their existing compliance with GMP, towards full WHO GMP compliance. The risk assessment of the companies (refer to section 4.4.2) revealed that the majority of pharmaceutical manufacturers have been rated as class "C", meaning "high risk companies", mainly due to the high risk associated with their sites. Phase I focuses on the establishment of WHO GMP compliant sites and on those quality management systems which showed severest deficiencies from WHO GMP. Using the results of the risk assessment the majority of currently class "C" rated companies following the phased roadmap approach should reach a "B" rating at the end of phase I as their sites, which have been a main reason for their low GMP compliance rating, should be in line with WHO GMP requirements at the end of this phase. Besides, those key quality elements for which the majority of companies showed least compliance will be in line with WHO GMP requirements at the end of phase I, enabling companies to have at least a sporadic implementation of QMS in place. During phase II the main focus will be on establishment of a comprehensive WHO GMP compliant QMS so that after completion of phase II both, structural ("site") and organizational measures ("QMS") for GMP compliance will be in line with WHO GMP and hence the companies will be operating in line with WHO GMP.

Figure 5: Graphical display of focus during the phases of the Kenya GMP Roadmap



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

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



Based on the results obtained from the WHO GMP compliance assessment of the Kenyan pharmaceutical manufacturers and the phases defined as above, a detailed technical roadmap has been developed outlining required actions and milestones:

- For improvement of Site related GMP aspects; and
- For improvement of QMS related GMP aspects throughout the phases of the roadmap.

The Kenya GMP Roadmap presents for each GMP relevant aspect:

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

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

The Kenya GMP Roadmap was agreed and endorsed by the key stakeholders including representatives from industry and government (both policymakers and regulators) following a series of meetings in 2013 and 2014.

5.2 Utilization of the roadmap

The Kenya GMP Roadmap has been developed based on the results from on-site assessments of Kenyan pharmaceutical manufacturers and has been tailored to the specific situation in Kenya. The technical reference standard for the roadmap is WHO GMP as outlined in the document "Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2, 2nd updated edition. Good manufacturing practices and inspection. World Health Organization, Geneva, 2007" as subsequently updated through the WHO Technical Report Series (TRS) especially TRS 961, Annex 3. The roadmap is intended to be a guiding tool encompassing the development and implementation requirements for site and quality management systems in line with WHO GMP and, as previously mentioned, should be read in conjunction with respective WHO GMP guidelines. The roadmap should be used as a stepwise tool to guide companies and regulatory authorities on the path towards WHO GMP:

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

5.3 Targeted timeframe for implementation

For an individual company, the timeframe for implementation of the roadmap is highly dependent on the existing GMP compliance of the manufacturer, as well as on available financial, technical and human resource capacities.

Initially, a targeted timeframe for implementation in the range of 5-7 years in total was proposed and discussed. A timeframe shorter than 5 years was unlikely for most of the manufacturers and could only be achieved in cases in which technology transfers are taking place, or an already relatively advanced GMP compliance level exists. On the other hand, the timeframe should not exceed 7 years as this bears the risk that the focus during the project might get lost, or project objectives might need to be changed significantly towards the end of the project.

During stakeholder meetings in 2013 it was agreed amongst all stakeholders including representatives from industry and the government (both policymakers and regulators) that the targeted timeframe for the entire project should be 5 years, whereby:

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

The time allocated to phase I is longer due to the need for modification of existing sites or construction of new sites during this phase.

Although the targeted timeframe of this roadmap has been agreed to be 5 years, it was acknowledged that the roadmap has to be viewed as a working document during its implementation. It was also acknowledged that there is a need for continued development of the implementation plan and for monitoring and review of the implementation process by a steering committee or similar body.

6. Implementation plan

During the development of the Kenya GMP Roadmap it became clear that there is a need for an implementation plan embracing multiple facets required for successful implementation of the roadmap, including the definition of near- and mid-term requirements. Aspects which needed to be addressed in this implementation plan included:

- Assurance of commitment of key stakeholders from private sector and government towards implementation of the roadmap;
- Establishment of a steering committee in order to ensure adherence of stakeholders to the GMP roadmap and to monitor and review the implementation process;
- Review of licensing standards by the regulatory authority in order to be in line with the roadmap requirements;

- Need for individual pharmaceutical manufacturers to perform internal technical assessments identifying their gaps as related to the GMP roadmap requirements, and to develop action plans to close these gaps;
- Development of incentive packages that include:
    - incentives currently available and assessment of their applicability;
    - new proposals demonstrating clear public benefit;
- Access to affordable finance, especially in the context of construction/modification of manufacturing sites, in order to comply with WHO GMP;
- Development of adequate and sustainable educational technical curricula enabling staff working in pharmaceutical industry and related governmental bodies to understand and implement WHO GMP requirements;
- Possibilities for networking between industrial pharmaceutical manufacturers.

In conjunction with key stakeholders from private sector and governmental bodies an implementation plan has therefore been developed. This accounts for key aspects that need to be considered in order to ensure successful implementation of the Kenya GMP Roadmap. The implementation plan covers key considerations for the defined activities, the stakeholders involved and the desired timeframes. The implementation plan covers various aspects including administrative aspects (e.g. establishment of a steering committee/working groups overseeing the implementation process), technical aspects (e.g. definition of minimum standards for licensing, the need for individual pharmaceutical manufacturers to perform gap analysis between the current and targeted GMP level, involvement of the regulatory authority and layout review), financial and incentives related aspects (e.g. budget assessment, development of incentive packages, access to affordable finance), human resource related aspects (e.g. review of academic curricula to be in line with industry demand), advocacy and communication related aspects (e.g. the development of medium and high level governmental support for the roadmap) as well as the promotion of cooperation between industrial pharmaceutical manufacturers. The implementation plan is provided in Annex B.

ANNEX A: KENYA GMP ROADMAP – TECHNICAL SPECIFICS

The technical specifics of the Kenya GMP Roadmap document were developed following a baseline assessment of Kenyan pharmaceutical manufacturers regarding their existing level of compliance to WHO GMP.

Based on results obtained from these company assessments a phased, risk-based approach to compliance with WHO GMP[7] has been developed. The baseline assessment revealed that site related GMP aspects need to be priority aspects for improvement, but also that immediate measures are required in order to reduce risks caused by the quality management system (QMS).

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

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

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

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

7 The technical reference standard for the roadmap is WHO GMP as outlined in the document "Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2, 2nd updated edition. Good manufacturing practices and inspection. World Health Organization, Geneva, 2007" as subsequently updated through the WHO Technical Report Series (TRS) especially TRS 961, Annex 3. The roadmap intends to be a guiding tool of what has to be done to develop and implement requirements for site and quality management systems in line with WHO GMP and shall be read in conjunction with respective WHO GMP guidelines.

START: SITE AND QUALITY MANAGEMENT SYSTEMS NOT IN COMPLIANCE WITH WHO GMP REQUIREMENTS

SECTION 1.1: PHASE I, SITE

Phase/ Reference number	*Key quality element*	*Actions for implementation*	*Milestones*
1.1.1	Premises**	Define scope of premises by taking into account: • Environment in which the premises are built • Targeted product classes (e.g. if toxic, sensitizing, mutagenic, beta-lactams, sensitive to light, temperature and/or humidity) • 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 raw materials, packaging, intermediate products, finished products • Product development activities to be performed at site ("pure" manufacturing site vs. R&D/scale-up plus manufacturing) • Process ancillary, technical and social areas • Availability, generation and distribution of utilities • Administrative areas (e.g. for record keeping, archiving, training) • Total area of land The design of a typical stand alone facility typically includes following areas: • Warehousing including receipt and dispatch areas • Clean sampling, dispensing and process rooms • Clean support areas (such as washing, movements and staging) • Packaging areas • Quality control laboratory • Process ancillary areas and equipment • Utilities	Scope of the premises defined.

Phase/ Reference number	***Key quality element***	***Actions for implementation***	***Milestones***
1.1.1	Premises** (ctd.)	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 • Avoid contamination and cross-contamination • Define suitable construction materials • Provide suitable environment for all operations taking place at site • Provide separation of manufacturing operations performed at site • Permit effective maintenance • Permit adequate space for operations taking place • Prevent access of unauthorized personnel from entering site • Within the site prevent access of unauthorized personnel to production, storage areas and the quality control laboratory • Provide airlocks for personnel and material • Ensure separation of controlled from uncontrolled areas • Allow effective pest control • Protect materials and products during receiving and dispatch procedures from weather and pest intrusion • Provide utilities required and suitable space for generation and distribution • Provide back-up power to run essential operations in the event of power failures • Provide suitable technical controls to prevent cross-contamination • 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 for separation of Quality Control laboratories from production areas • Provide separation of rest and refreshment room from manufacturing and control areas	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.

Phase/ Reference number	***Key quality element***	***Actions for implementation***	***Milestones***
1.1.1	Premises** (ctd.)	• Provide separation of warehouses for raw material, packaging materials and finished goods from production areas • Provide separation of maintenance workshops from production areas Establishment of suitable contractors* and support staff for construction of site. Construction of premises complying to the design specifications.	Suitable contractors and support staff identified and contracted. Premises complying with predefined specifications in place. Facility, as constructed, is conforming to original design drawings.
1.1.2	Utilities impacting Good Manufacturing Practice	<u>Water</u>: Establishment 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 purified water. 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	Suitable water source (e.g. borehole or public water) established. 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.

Phase/ Reference number	***Key quality element***	***Actions for implementation***	***Milestones***
1.1.2	Utilities impacting Good Manufacturing Practice	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 to the design specifications. <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. 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 pressure cascades, temperature, humidity, acceptable number of particulates, air changes) are defined. The design and extent of the environmental control are based on a clean room concept and assure that an environment suitable for pharmaceutical manufacturing procedures performed and products handled at site is created. The system is designed to prevent the areas within the factory from cross-contamination and contamination as well it prevents contamination of the environment outside the factory. The design of the system is suitable for the clean room concept selected for the facility and allows monitoring of pressure cascades and environmental attributes.	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 original design drawings. Assessment performed. Requirements for environmental controls defined. Design specifications and layout of Heating, Ventilation, Air Conditioning units available. The system allows monitoring of critical attributes such as pressure cascades, environmental attributes.

Phase/ Reference number	***Key quality element***	***Actions for implementation***	***Milestones***
1.1.2	Utilities impacting Good Manufacturing Practice	Establishment of suitable supplier(s)* for Heating, Ventilation, Air conditioning systems	Suitable supplier(s) identified and contracts available.
		Installation/Commissioning of the Heating, Ventilation, Air conditioning and distribution systems complying to the design specifications.	Heating, Ventilation, Air conditioning and distribution systems complying with predefined specifications and design in place. As-built systems conform to original design drawings.
		Compressed Dried Air (CDA): Based on the intended use(s) of CDA, required quality(s) are defined.	Requirements for CDA defined including intended use(s) and quality(s).
		Taking into account the environment(s) in which CDA is utilized, required pressures and volumes at site and product groups manufactured, the CDA system is designed to remove contaminants such as oil, water, particles and bio burden to the extend required and allows monitoring of critical attributes such as pressure and dew point.	Design specifications and layout of CDA system available. The system has provisions for monitoring of critical attributes.
		Establishment of suitable supplier(s)* for CDA system(s).	Suitable supplier(s) identified and contracts available.
		Installation/Commissioning of the CDA generation and distribution system(s) complying to the design specifications.	CDA generation and distribution system(s) complying with predefined specifications and design in place. As-built system conforms to original design drawings.

Phase/ Reference number	***Key quality element***	***Actions for implementation***	***Milestones***
1.1.2	Utilities impacting Good Manufacturing Practice	<u>Steam</u> Evaluation of the need for steam generation and distribution system(s). Based on the intended use(s) of steam, required quality(s) are 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. Establishment of suitable supplier(s)* for steam system(s). Installation/Commissioning of the steam generation and distribution system(s) complying to the design specifications.	Evaluation regarding the need for steam system(s) finalized. Intended use(s) of steam and steam qualities defined. Design specifications and layout of steam system available. The system has provisions for monitoring of critical attributes. Suitable supplier(s) identified and contracts available. Steam generation and distribution system(s) complying with predefined specifications and design in place. As-built system conforms to original design drawings.
1.1.3	Equipment	Definition of dosage forms to be manufactured, operational and control procedures to be performed at the site and production capacity. Definition of specifications, design and location of equipment to assure suitability of the equipment for its intended purpose taking into consideration requirements such as: • Smooth finishes • Right quality of construction materials assuring that surfaces with product contact are not reactive, additive, absorptive or adsorptive	Dosage forms and operational and control procedures performed at site and targeted production capacity defined. Design specifications and layout/ drawings of equipment and support systems available.

Phase/ Reference number	***Key quality element***	***Actions for implementation***	***Milestones***
1.1.3	Equipment (ctd.)	• Cleanability • Prevention of (cross-) contamination • Maintenance which should have as little impact on clean room production processes as possible (e.g. by "through the wall" installations) • Ease of change-over • Use of suitable lubricants and coolants • Suitability of equipment for calibration procedures • Type and quality of calibration standards needed • Appropriate range and precision of measuring equipments • Appropriate equipment number and capacity of equipment taking into consideration change-over and process cycle times • Operation environment • Required space and access to equipment for operation • Utilities/support systems needed for operation • Safety of operation • Need for adequate labelling at point of operation Establishment of suitable supplier(s)* for equipment. Installation/Commissioning of equipment complying to the design specifications.	Suitable supplier(s) identified and contracts available. Equipment complying with predefined specifications and design in place. As-built equipment conforms to original design drawings.
1.1.4	Personnel/ Personal hygiene	Based on product range, operational steps and production capacity define the number and qualification of personnel required. Taking into consideration the product range, the operations to be performed at the site and the number and qualifications of personnel required at site the design of site and equipment have to assure that:	Number and qualification of personnel defined. Design specifications and layout for premises and equipment are suitable with regards to personnel and hygiene.

Phase/ Reference number	***Key quality element***	***Actions for implementation***	***Milestones***
1.1.4	Personnel/ Personal hygiene (ctd.)	• Rest and refreshment rooms are separated from production and control areas with no direct access to them • 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.	Implementation is done complying with original specifications and designs. Suitable garments for staff defined and implemented.
1.1.5	Material handling	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 and cleanability to avoid any alteration of material and product during storage. The design has to ensure 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	Design specifications and layout for storage and material transport are in place. Implementation is done complying with original specifications and designs.

Phase/ Reference number	***Key quality element***	***Actions for implementation***	***Milestones***
1.1.5	Material handling (ctd.)	to be restricted to authorized personnel. Based on the product classes manufactured, the manufacturing procedures and the production capacity of the site a suitable flow of material and product through the various manufacturing steps is defined.	
1.1.6	Quality control	Definition of analytical activities which have to take place in the quality control laboratory based on the product range and manufacturing activities performed at the site. Design of layout of the laboratory and definition of equipment required to perform all analytical controls effectively and reliably are carried out taking into consideration: • Separation of quality control laboratory from production areas • Restriction of access to laboratory and its storage areas • Adequate space, environment and equipment to prevent mix-ups and cross-contaminations during sampling, inspecting, testing of starting materials, packaging materials, intermediate, bulk, finished 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	Analytical activities defined. Design specifications and layout for premises and equipment are suitable for performance of quality control activities.

Phase/ Reference number	***Key quality element***	***Actions for implementation***	***Milestones***
1.1.6	Quality control (ctd.)	• Suitability of storage areas with focus on size, safety and environment for storage of reagents, 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 equipments • Suitability of equipments for required calibration, qualification procedures • Type and quality of calibration standards needed • Safety of operations • Availability of emergency equipment • Appropriate waste handling Establishment of suitable contractors* and supplier(s)* for construction, equipment procurement, and servicing of laboratory. Design and equipment of laboratory complying to the design specifications and layouts.	Suitable contractors and suppliers identified and contracts available. Design and specifications of laboratory and equipment complying with original design and specifications.
END OF SECTION: PHASE I, SITE			

SITE COMPLIANT WITH WHO GMP BUT QUALITY MANAGEMENT SYSTEMS NOT IN LINE WITH WHO GMP

SECTION 1.2: PHASE I, QUALITY MANAGEMENT SYSTEMS

Phase/ Reference number	***Key quality element***	***Actions for implementation***	***Milestones***
1.2.1	Quality assurance	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.	Authorized organizational charts in place.
		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.	Documented quality management system in place and implemented.
		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) • Production and control operations	Written procedures for quality assurance in place and implemented.
		Development and implementation of a system for quality risk management defining applicability, responsibilities and procedures.	Quality risk management system in place and implemented.

Phase/ Reference number	***Key quality element***	***Actions for implementation***	***Milestones***
1.2.2	Utilities impacting Good Manufacturing Practice	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 equipments including records/logbooks for each equipment.	Documented procedures for operation of equipments 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 and sampling frequencies.	Documented specifications, sampling procedures and frequencies in place and implemented.
		Establishment of a continuous monitoring and reporting program for utilities directly impacting product quality.	A program for continuous monitoring and reporting in place and followed.

Phase/ Reference number	***Key quality element***	***Actions for implementation***	***Milestones***
1.2.3	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. Development of a cleaning program outlining requirements and training needs of personnel, premises, equipment, material, garments to be cleaned, cleaning procedures, cleaning frequencies, cleaning and disinfection agents. This program has to be accompanied by a schedule and a log to trace the activities done. Development of an environmental monitoring program including specifications, action and alert limits, sampling procedures and frequencies for baseline and continuous evaluation.	Suitable cleaning procedures developed and successfully validated. A comprehensive cleaning program including schedule and logs is in place and followed. Environmental monitoring programs are developed and implemented.
1.2.4	Qualification and validation	Development and implementation of master documentation for calibration, qualification and validation activities (Validation master plan and Project plans) outlining approach, procedures, responsibilities and documentation requirements assuring that only calibrated/qualified equipment is used for production. 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 building, utilities, equipment, inventory 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.

Phase/ Reference number	***Key quality element***	***Actions for implementation***	***Milestones***
1.2.5	Premises	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 (clean, in operation, awaiting cleaning, under maintenance) within operational sections.	Documented system for defining room status in place and implemented.
1.2.6	Equipment	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 including records/ logbooks in place and implemented.
1.2.7	Material handling	Development and implementation of documented systems for receipt, handling, sampling, inspecting, testing, release, rejection and destruction of materials, labels, intermediates and finished products and defining authorized personnel performing these operations including: • Definition and implementation of procedures for sampling, identity and integrity check of incoming consignments	

Phase/ Reference number	***Key quality element***	***Actions for implementation***	***Milestones***
1.2.7	Material Handling (ctd.)	• Definition and implementation of procedures for handling and labelling materials, labels, intermediates and products according to their status including authorized personnel for access and status change • Development and implementation of a system for unique identification of materials, labels, intermediates and products including identification code, sampling status, storage location and number of containers • Definition and implementation of procedures for stock rotation (e.g. first-expiry-first-out) and expiry control • Definition and implementation of procedures for regular stock reconciliation comparing actual versus recorded stocks • Definition and implementation of procedures to ensure the storage of materials in a suitable environment with restriction of access where necessary • Definition and implementation of procedures for issuing and reconciliation of materials, labels, intermediates and products • Definition and implementation of procedures to avoid contamination of equipment and materials by agents used for pest control • Definition and implementation of procedures for proper and safe storage and disposal of waste	Documented systems for receipt, handling, sampling, testing, release, rejection and destruction of materials, labels, intermediates and finished products in place and implemented.
1.2.8	Quality Control	Development and implementation of procedures, records and registers covering all operations performed in the laboratory 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,	Procedures, records and registers covering all operations performed in the laboratory in place and implemented including: Documented procedures including records and logs for the entire sample flow allowing full traceability.

Phase/ Reference number	***Key quality element***	***Actions for implementation***	***Milestones***
1.2.8	Quality control (ctd.)	standards/reagents and quality thereof, equipments, methods, personnel involved	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, equipments, 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 equipments, methods used	Procedures, logs and records for operation and suitability testing of equipments, methods used in place and implemented.
		• Development and implementation of issuing procedures and records for samples, standards, reagents and controlled documents	Issuing procedures and records for samples, standards, reagents and controlled documents in place and implemented.
		• Development and implementation of procedures and records for stock control	Procedures and records for stock control in place and implemented.

Phase/ Reference number	***Key quality element***	***Actions for implementation***	***Milestones***
1.2.8	Quality Control (ctd.)	• Development and implementation of procedures for handling of test results including raw data and worksheets/laboratory notebooks, records	Procedures for handling of test results including raw data and worksheets/ laboratory notebooks, records 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 procedures, records and logs for handling of reagents/solvents, culture media including required quality, identification of suppliers, receipt, identification/labelling, storage, expiration dating, issuance, use, master formulae for preparations of reagents and culture media, procedures for standardization and suitability testing where appropriate	Procedures, records and logs for handling of reagents/ solvents, culture media including required quality, identification of suppliers, receipt, identification/ labelling, storage, expiration dating, issuance, use, master formulae for preparations of reagents and culture media, procedures for standardization and suitability testing where appropriate in place and implemented.
		• Development and implementation of documented procedures, records and logs for handling of chemical reference standards including source, procurement, receipt, labelling, storage, issuance, use, duration of use	Documented procedures, records and logs for handling of chemical reference standards in place and implemented.
		• Development and implementation of documented procedures for preparation and handling of chemical working standards including reference material, preparation, initial and regular checking of potency, labelling, storage, issuance, use, duration of use	Documented procedures, records and logs for handling of working reference standards in place and implemented.

Phase/ Reference number	***Key quality element***	***Actions for implementation***	***Milestones***
1.2.8	Quality Control (ctd.)	• Development and implementation of procedures for handling of out of specification results (OOS) and out of trend results (OOT) including laboratory investigations, number of retests and further investigation	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 requirements	Stability programs in place and implemented in line with WHO requirements.
		• Development and implementation of a system for drawing, handling storage and inspection of retention samples	System for drawing, handling, storage and inspection of retention samples in place and implemented.
		• Definition and implementation of appropriate garment and safety procedures for protection of operator and environment and to avoid any contamination of samples	Appropriate garment and safety procedures in place and implemented.
		• Development and implementation of procedures for waste handling	Procedures for waste handling in place and implemented.
END OF SECTION: PHASE I, QMS			

SITE AND QMS IDENTIFIED HAVING MOST CRITICAL IMPACT ON PRODUCT SAFETY, QUALITY AND EFFICACY IN KENYA COMPLIANT WITH WHO GMP

SECTION 2: PHASE II

Phase/ Reference number	***Key quality element***	***Actions for implementation***	***Milestones***
2.1	Complaints	Development and implementation of a documented system regarding handling, investigation, corrective and preventive actions of complaints containing: • Responsible person(s) and responsibilities • Procedures to be followed for handling, investigation, corrective and preventive actions of complaints including timelines • The need to extend investigation to other batches, materials, products • Investigation of possible counterfeiting • The need for product recall • The need to inform competent authorities and public in case of a public risk • Registration system for complaints received, investigations and actions performed • Regular review and trending of records	Documented system for handling, investigation, corrective and preventive actions of complaints in place and implemented.
2.2	Product recalls	Development and implementation of a documented recall procedure containing: • Responsibilities of personnel involved in recall procedure/composition of Recall committee • Classification of recall and actions to be taken based on the severity of reason for the recall including timelines • The need to inform competent authorities and public in a timely manner in case of public risk • Procedures to be followed for handling, investigation and corrective and preventive actions • The need to extend investigation to other batches, materials, products • Reconciliation of recall • Registration system for recall and activities performed to the recalls • Storage and labelling of recalled products • Procedures to verify suitability of recall system	Documented system for recall procedure in place and implemented.

Phase/ Reference number	***Key quality element***	***Actions for implementation***	***Milestones***
2.3	Contract production and analysis	Based on product range and analytical requirements evaluation of the need for contract production and/or analysis is done. Development and implementation of documented procedures to ensure that contract production and analysis is performed in accordance to the marketing authorization of the product and in line with GMP requirements containing: • Pre-requisites to be fulfilled before contract production/analysis takes place including evaluation of potential contract acceptor regarding legality, suitability and competence • Written agreements between contract giver and acceptor detailing responsibilities, knowledge management, attributes impacting quality of product/service, release and documentation procedures, continuous re-evaluation of contract acceptor • List of approved contract organizations	Needs for contract production/analysis identified. Documented procedures for contract production/analysis in place and implemented.
2.4	Self-inspection and quality audits	Development and implementation of a system for self-inspections including: • Inspection program • Inspection frequency • Composition of inspection team, training requirements and responsibilities • Record and classification of audit observations • Reporting of observations • Corrective and preventive actions • Evaluation of effectiveness of actions taken Development and implementation of a system for manufacturer/supplier audits and approval including: • Procedure for evaluation of compliance of manufacturers/suppliers of starting and packaging materials with established specifications • Procedure for evaluation of compliance of manufacturers/suppliers of starting and packaging materials with established manufacturing procedures and regulatory requirements • Audit procedures for manufacturers/suppliers • Requirement to establish quality/technical agreements with manufacturers/suppliers • A list of approved manufacturers/suppliers for starting and packaging materials	Self-inspection procedures developed and implemented. Procedures for manufacturer/supplier audits in place and implemented.

Phase/ Reference number	***Key quality element***	***Actions for implementation***	***Milestones***
2.5	Personnel	Establishment of adequate number of personnel required and development of written procedures for establishment of job descriptions. Definition of necessary qualifications, experiences and responsibilities in form of job descriptions ensuring that key personnel responsible for supervising the production and quality unit(s) for pharmaceutical products possesses the qualifications of a scientific education and practical experience required by national legislation. Development and implementation of mechanisms and procedures for restriction of access to site, production, storage and quality control laboratory.	Number, qualifications and experience of personnel defined. Signed and dated job descriptions for personnel in place. Mechanisms and procedures in place and implemented for restriction of access.
2.6	Training	Development and implementation of documented training procedures including: • Training needs assessment • Training program and schedule for initial and continuous training • 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	Training procedures in place and implemented.

Phase/ Reference number	***Key quality element***	***Actions for implementation***	***Milestones***
2.7	Personal hygiene	Development and implementation of documented procedures to ensure GMP-conform personal hygiene including: • Entrance and exit procedures for the various sections of the site which are suitable to prevent (cross-) contamination especially in cases where sensitizing/hazardous products are manufactured • Suitable protective clothing concept for the various sections of work • Separate protective clothing for areas in which sensitizing/hazardous products are manufactured • Suitable laundering procedures to prevent contamination of garment during laundry and drying • Signs visualizing hygienic requirements such as washing, sanitization and gowning procedures • Health examination program for personnel at beginning of employment and at defined frequencies • 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	Documented procedures ensuring GMP-conform personal hygiene in place and implemented.
2.8	Documentation	Development and implementation of a documentation system containing: • Master documents defining design, preparation, multiplication without alteration, issuance and distribution to the place(s) of use, traceability, review and authorization, storage, archiving and destruction of documents • Definitions for GMP-conform corrections and alterations • A system for document and data control in electronic media (access control, authorizations for data entries and changes)	Comprehensive documentation system in place and implemented.

Phase/ Reference number	***Key quality element***	***Actions for implementation***	***Milestones***
2.8	Documentation (ctd.)	• A master index of all company procedures, forms and current version numbers allowing traceability of revision history • Documentation systems defining date and time conventions, specifications, procedures, logs and records for all type of materials, products, operations, methods of manufacturing, controls, maintenance, cleaning, sanitization and labelling including authorities and responsibilities of personnel involved	
2.9	Good practices in production	Definition of manufacturing procedures and processes performed. Development and implementation of written procedures for all manufacturing and packaging activities carried out, also reflecting results of qualifications/validations performed. Development and implementation of documented master formulae, manufacturing and packaging procedures, records and registers for each product and batch size manufactured including in-process and environmental controls, line-clearance and reconciliation procedures allowing full traceability of batch history.	Manufacturing procedures and processes defined. Written procedures for all manufacturing activities carried out, also reflecting results of qualifications/validations performed in place and implemented. Documented master formulae, manufacturing and packaging procedures, records and registers for each product and batch size manufactured including in-process

Phase/ Reference number	*Key quality element*	*Actions for implementation*	*Milestones*
2.9	Good practices in production (ctd.)		and environmental controls, line-clearance and reconciliation procedures allowing full traceability of batch history in place and implemented.
		Development and implementation of labelling practices of materials, containers, equipment, rooms, lines identifying product/material processed, strength, batch number, production stage and details of previous product/material.	Labelling practices in place and implemented.
		Development and implementation of organizational procedures to avoid contamination and cross-contamination.	Organizational procedures to avoid contamination and cross-contamination 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.
END OF SECTION: PHASE II			

COMPLETION: SITE AND QUALITY MANAGEMENT SYSTEMS IN COMPLIANCE WITH WHO GMP

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

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

ANNEX B: IMPLEMENTATION PLAN

The implementation plan has been developed in conjunction with key stakeholders from the private sector and governmental bodies. It takes into consideration key aspects which need to be considered to allow implementation of the Kenya GMP Roadmap, within the context of the wider Kenya Pharmaceutical Sector Development Strategy (KPSDS).

The implementation plan includes key considerations for activities, the various key stakeholders involved, and potential timeframes. The implementation plan covers various areas, many of which link up to the core seven KPSDS components. These areas covered by the plan include:

- Administrative aspects;
- Technical aspects;
- Financial and incentives related aspects;
- Human resource related aspects;
- Advocacy and communication related aspects;
- Industrial cooperation related aspects.

Abbreviations used in the implementation plan:

HR	Human Resources
MEAC	Ministry of East African Community
MOH	Ministry of Health
MOIED	Ministry of Industrialization and Enterprise Development
N/A	Not Applicable
PPOA	Public Procurement Oversight Authority
Q	Quarter
QMS	Quality Management System
RA	Regulatory Authority
TOR	Terms of Reference
UNIDO	United Nations Industrial Development Organization
Y	Year

Serial Number	***Reference to KPSDS***	***Key Aspect***	***Activities for Implementation of GMP Roadmap***	***Key Success Indicators/ Milestone***	***Responsible Stakeholder(s)***	***Timeline^***
1	N/A	Establishment of Supervisory Bodies	Define overall steering committee for KPSDS – composition & TORs	Overall steering committee and Roadmap working group in place and fully operational based on defined TORs	MOIED, MOH/ RA, UNIDO, Industry	1 Q, 1.Y
			Define Roadmap working group & composition; TORs incl. roadmap implementation review		MOIED, MOH/ RA, UNIDO, Industry	1 Q, 1.Y
			Monitoring of compliance to Roadmap	Steering committee and working group have the authority to ensure compliance of stakeholders with Roadmap. A procedure for monitoring compliance developed by the steering committee is in place and adhered to	Steering committee	Annual review

^ from launch of Roadmap

Serial Number	***Reference to KPSDS***	***Key Aspect***	***Activities for Implementation of GMP Roadmap***	***Key Success Indicators/ Milestone***	***Responsible Stakeholder(s)***	***Timeline^***
2	SC1: GMP RM	Regulatory aspects	Development of pre-licensing procedure for manufacturers with regard to site modifications/new buildings (based on layout review)	A pre-licensing procedure has been developed	RA	1-2 Q, 1.Y
			Categorization of companies based on criticality of products/site/QMS [relates to minimum requirements]	A risk categorization has been developed by RA forming an integral part for classification of audit observations	RA	3-4 Q, 1.Y
			Define minimum standards for license throughout project – based on above criticality assessment	Risk-based minimum licensing standards for companies throughout the project defined enforcing compliance of pharmaceutical companies with GMP Roadmap and ultimately ensuring compliance with WHO GMP at the end of the project	RA	3-4 Q, 1.Y
3	SC1: GMP RM	Implementation of Gap analyses/ CAPAs	Sourcing for service providers giving technical assistance for CAPA development, where necessary	Suitable service providers identified and technical assistance provided, where necessary	Industry	1-2 Q, 1Y
			Gap analysis performed by companies regarding compliance to WHO GMP/risk mitigation of existing site/ QMS during transitional period until commencement of new site, where necessary	CAPAs in place; presented to/agreed by RA	Individual companies to perform GAP analysis/ CAPAs; supervision/facilitation by RA	3-4 Q, 1.Y

^ from launch of Roadmap

Serial Number	***Reference to KPSDS***	***Key Aspect***	***Activities for Implementation of GMP Roadmap***	***Key Success Indicators/ Milestone***	***Responsible Stakeholder(s)***	***Timeline^***
4	SC5: Incentives	Availability of incentives	Identify MS/steps in development which can be linked to qualification for incentives (linked to risk assessment)	A proposal for an incentive scheme based on compliance to WHO GMP is ready for presentation to treasury/ external financing bodies	MOIED, MOH/RA, UNIDO, Industry	1-2 Q, 1.Y
			Budget and impact assessment for GMP Roadmap (Treasury contribution/external financing)	Budget and impact assessment for GMP roadmap available pointing out financial requirements, possibilities, opportunities and challenges	MOIED, MOH	2 Q, 1.Y
			Development of incentives package for improvement to WHO GMP	Based on the budget and impact assessment a viable incentive package has been developed and is available to industry based on their adherence to the GMP Roadmap	MOIED, MOH	3 Q, 1.Y
			Exploration of special economic zones for construction of new sites	Special economic development zones suitable for pharmaceutical industry identified; pharmaceutical industry is aware and has access to these zones	MOIED	1 Q, 1.Y
			Exploration of market protection based approaches, e.g. evaluation of suitability of import controls in order to promote local manufacturing	Possibilities for import controls explored and proposal	MOIED, MEAC, MOH/ RA	2 Q, 1.Y

^ from launch of Roadmap

Serial Number	***Reference to KPSDS***	***Key Aspect***	***Activities for Implementation of GMP Roadmap***	***Key Success Indicators/ Milestone***	***Responsible Stakeholder(s)***	***Timeline^***
5	SC4: Finance	Access to finance for individual companies (Refer to KPSDS – strategic component)	Evaluation of access to affordable finance including government organs	Strategy for affordable finance developed and ready for implementation	MOIED/UNIDO, Steering committee	Recognized priority; commencing from 1 Q, 1.Y
6	SC6: HR	HR development (Refer to KPSDS – strategic component)	HR needs assessment (motivation + capacity)	HR requirements for implementation of GMP roadmap and gaps of current situation identified; Implementation plan for strategic component "HR development" in place	Steering committee	4 Q, 1.Y
			Review of curricula to be in tandem with pharmaceutical industry needs (academic and post-academic skills development, continuous training)	Reviewed curricula ensuring adequate capacity development for implementation of GMP roadmap	RA	1-2 Q, 2.Y
			Identification & establishment of resource & training centers	Resource and training centers identified/ established ensuring adequate capacity development for roadmap implementation	Steering committee	TBD

^ from launch of Roadmap

Serial Number	*Reference to KPSDS*	*Key Aspect*	*Activities for Implementation of GMP Roadmap*	*Key Success Indicators/ Milestone*	*Responsible Stakeholder(s)*	*Timeline^*
7	N/A	Advocacy & communication	Engagement of shareholders & commitment to Roadmap	Shareholders aware of key dimensions of the GMP Roadmap and fully committed towards implementation	Industry	1 Q, 1.Y
			Development of mid and high level Govt. support for Roadmap (county and national)/ Vision 2030/ buy Kenya/ PPOA and KEMSA	Concept and benefits of GMP Roadmap communicated to mid and high level governmental bodies; GMP Roadmap supported at mid and high governmental level	MOIED/UNIDO, Steering committee	1 Q, 1.Y
			Development of a communication strategy encompassing all levels of stakeholders	Communication strategy developed and ready for implementation	MOIED/UNIDO, Steering committee	2. Q, 1.Y
			National launch of the Roadmap	Roadmap launched	MOIED/UNIDO, MOH, RA	3.Quarter of 2014
8	N/A	Promotion of industry cooperation	Creation of platform for exchange of services/supplier/vendor information/ recommendations/overseas vendor audit reports	Platform for networking/ cooperation amongst industrial players established	Industry	2 Q, 1.Y – 1.Q 2.Y

^ from launch of Roadmap

APPENDIX I: KEY QUALITY ELEMENTS AND FOCUS OF COMPANY ASSESSMENTS

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

WHO GMP requirements have been defined in 17 key quality elements. Each key quality element has been divided into sub-sections for which the assessment focus had been defined. Key quality elements together with defined subsections and the focus during assessment of the key quality elements are outlined in Table 4.

Table 4: Key quality elements, defined subsections and focus during assessment

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

Key quality elements	***Subsections***	***Focus during assessment***
1. Quality Assurance System (ctd.)	Change Control	• Applicability of procedure • Responsibilities • System for request, evaluation/classification, implementation, evaluation of effectiveness, close-out • Records, trending

	Regular evaluations of product quality	• Product Quality Review
		  • Applicability of procedure
		  • Responsibilities
		  • Procedure for product quality review/annual product review, frequency, content, trending, conclusions drawn
		• Self-inspection procedures (details point 8)

	Quality Risk Management	• Applicability • Responsibilities • Procedure • Documentation

2. Utilities impacting GMP requirements	HVAC	• Need for separate systems
		• Level of filtration (filter specifications)
		• Recirculation or fresh air
		• Location of filters
		• Position of inlet and air return, dust extractors
		• Room classifications
		  • Temperature
		  • Humidity
		  • Air changes
		  • Particulates
		  • Microbes
		• Pressure differentials
		• Design of ducting
		• Easy and effective cleaning
		• Alarm system
		• Air flow direction
		• Compliance of design specifications and drawings with reality
		• Qualification and re-qualification procedures
		• Labelling of ducting

Key quality elements	***Subsections***	***Focus during assessment***
2. Utilities impacting GMP requirements (ctd.)	HVAC (ctd.)	• Monitoring of HVAC system (e.g. particles, microbes, humidity, temperature, pressure differentials) • Operation, maintenance, calibration, SOPs, records for HVAC including breakdown/ emergency programs
	Purified 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
	Compressed dried air	• Generation of compressed dried air • Level of filtration (Filter specifications) • Location of filters • Water separation • Dew point • Design of ducting/distribution system • Easy and effective cleaning • Alarm system • Air flow direction • Capacity and daily demand • Compliance of design specifications and drawings with reality • Labelling of ducting • Qualification and re-qualification procedures • Monitoring of system (e.g. oil, particles, microbes, dew point, filter integrity) • Operation, maintenance, calibration, SOPs, records

Key quality elements	***Subsections***	***Focus during assessment***
3. Sanitation and hygiene	Sanitation and hygiene program	• Program in place including personnel, premises, equipment, materials, containers, cleaning/ disinfection agents, frequencies • Records, logs • Environmental monitoring program • Sanitization, disinfection of drains • Garment cleaning/laundry
4. Qualification and validation	Validation Master Plan	Approach, procedures, responsibilities and documentation requirements for calibration, qualification and validation activities
	Qualification/calibration of equipment	• Schedules • Calibration frequencies • Elements of qualification (IQ, OQ, PQ) • Protocols • Reports • Ratio of equipment qualified/calibrated to unqualified/not calibrated • Handling of non-qualified, non-calibrated equipment • Responsibilities • Standards used and traceability of standards • Tracking/labelling of calibration/qualification status
	Process validation	• Type of process validation in place • Plan • Protocols/reports

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

Key quality elements	***Subsections***	***Focus during assessment***
7. Contract production and analysis	Control of external contract work	• Responsibilities • Evaluation of contractors • Re-evaluation of contractors and frequency • Auditors and qualification • Recording, classification, reporting of observations • Contract/agreements • Records
8. Self-inspections and quality audits	Self inspections and quality audits for evaluation of regulatory and GMP compliance	• Frequency • Responsibilities • Auditors and qualification • Recording, classification, reporting of observations • CAPA program • Evaluation of effectiveness of CAPA
	Supplier audits and approval	• Responsibilities • Evaluation • Re-evaluation procedure and frequency • Auditors and qualification • Recording, classification, reporting of observations • Contract/agreements • List of approved suppliers/manufacturers
9. Personnel	Job descriptions	• SOP • Example job descriptions for key personnel • Authorities and key responsibilities • Signed by employer and staff
	Key personnel	• Qualifications, experience • 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 • 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, fire fighting equipment, etc.) • Health examination programs and frequencies
	Hygiene measures	• Entrance procedures • Protective clothing • Prohibition of eating, drinking and smoking material and personal medicines • Restrain of ill, contagious staff from working in open product areas
	Training	• External vs. internal training • As point 10
12. Premises	General	• Location • Design/layout and comparison with reality • Material of construction and finishes • Suitability for cleaning and sanitization • Written preventive maintenance and cleaning/sanitation procedures and records • Logical flow of materials, products and personnel

Key quality elements	***Subsections***	***Focus during assessment***
12. Premises (ctd.)	General (ctd.)	• Pest control
	Cleanliness zoning	• Clean zone concept • Separation of areas • Room status labelling • Material of pallets and furniture
	Ancillary areas	• Separation of rest and refreshment rooms form manufacturing and QC • Appropriate changing rooms • Toilets with no direct access to production/storage areas • Maintenance workshops separate from production
	Storage areas	• Capacity for proper storage and separation and control of various categories of materials/products and material/product status • Adequate storage conditions • 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 products • Cleanability and cleanliness • Environment
	Production areas	• Layout • Sequence of operations, clean zones • Space • Cleanability • 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	• Drawings of critical equipment and support systems • Support systems for power back-up and uninterrupted power supply (UPS) • Suitability for use, maintenance and cleaning • Maintenance procedures, schedules, logs • Cleaning procedures, logs • Calibration, qualification procedures, records/logs • Calibration standards • Labelling with calibration, qualification and operational status • Operating procedures/logs • Labelling of fixed pipeworks • Food grade status of lubricants/coolants in case of product contact
14. Materials (sourcing, control, storage and handling)	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

Key quality elements	***Subsections***	***Focus during assessment***
14. Materials (ctd.)	Starting materials	• Purchase, storage, handling and control • List of approved suppliers/manufacturers • Procedure defining storage conditions of starting materials • Material codes/company specific batch numbers • Procedure/checklist for receipt of materials • Identity of each container • Dispensing procedures and handling of dispensed materials • Sampling procedures
	Packaging materials (primary or printed packaging material)	• Purchase, storage, handling and control • Sampling procedures • Access control for printed PM • Use of feed rolls, indication of splicing • Handling of unused materials • Destruction
	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 • Distribution records
	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	• Records for receipt and preparation • Procedures, records for preparation, labelling, storage, handling and issuance • Controls to verify suitability of culture media

Key quality elements	***Subsections***	***Focus during assessment***
14. Materials (ctd.)	Reference standards	• Source, receipt, handling, storage and issuing of primary standards • Standardization, handling, labelling, storage and issuance of working standards
	Waste material	• Storage before disposal • Procedure, methods and frequency of disposal • Destruction of printed packaging materials and labels before disposal • Adherence to local laws/ regulations
15. Documentation	Defined instructions and procedures; system for elaboration, checking, approval and version control	• System/procedures/master documents • Responsibilities • Alteration and correction of documents • Distribution to places of use • Document/data control in electronic media
	Record keeping	• Systems for records in manufacturing, QC and distribution • Traceability of documents/batches
	Labels	• Practice for material, equipment, room identification and status control • Label control/issuance • Label content, initialization, dating
	Logbooks	• Availability for equipment, components, procedures, rooms • Referencing of logbooks/records to SOPs
	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

Key quality elements	***Subsections***	***Focus during assessment***
15. Documentation (ctd.)	Test records	• Design, content, review, authorization, distribution and version control practices • Handling of electronic data/data generated by computerized systems • Traceability • Methods for preparation of working documents from master documents
	Master formulae/Batch processing records	• Design, content, review, authorization, distribution and version control practices • Availability of documents, protocols and records for manufacturing including line clearance, sampling, testing, monitoring, review and release requirements with signatures and authorizations • Batch traceability • Methods for preparation of working documents from master • Recording of deviations
	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 • Recording of deviations • Reconciliation of labels and printed packaging material
	Cleaning/sanitization, maintenance procedures and records	• Schedules, documented procedures, records, logs for equipment and facilities
	SOPs and associated records	• System, incl. authorization and version control, prevention of use of unauthorized copies • Referencing of records/logs to related SOP • List of SOPs/master indices
	Archiving	• Requirements for various types of documents and records • Traceability/retrieval procedure for archived documents • Type/format for archiving • Storage conditions • Security/back-up policy

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
	Processing operations	• Access control to production premises • Segregation of operations • Exclusion of production of non-medical products • Recording of operations • Labelling • In process controls • Line clearance practices, incl. documentation • Reconciliation and investigation of reconciliation discrepancies
	Packaging operations	• Segregation of products • Measures to minimize risk of cross-contamination and mix-ups • Line clearance practices, incl. documentation • Check and recording of printing operations • Labelling practice • In process controls • Reconciliation and investigation of reconciliation discrepancies • SOP for return of unused materials to stock

Key quality elements	***Subsections***	***Focus during assessment***
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 • Retention samples: Handling, storage, registration, labelling, frequency of drawing of retention samples • OOS/OOT procedures • Servicing, maintenance procedures, agreements • Safety/waste handling
	QC of starting and packaging materials, labels, intermediates, bulk and finished products	• Handling and inspection of incoming materials • Test procedures, defined quality, specifications and records • Microbial testing, reference strains • Sampling procedures including receipt, registration, storage, issuance for testing • Cleaning of sampling tools • Handling, storage of reagents, standards • Logs, registers • Issuance of controlled documents • Calibration, qualification and validation • Labelling • Cleaning procedures • Traceability of sample history, standards/ reagents and quality thereof, equipments, methods, personnel
	Test requirements	• Requirements for testing starting, packaging materials, labels, intermediates, products • Release procedures, authorities • Approval/certification procedures • Evaluation of analyst performance • System suitability testing

Key quality elements	***Subsections***	***Focus during assessment***
17. Good practices in quality control (ctd.)	Batch record review	• Checklists • Certification procedure and authority
	Stability studies	• Stability testing programs • Protocols • Reports • Schedules • Registers • Stability conditions and monitoring of conditions • Establishment of shelf-life
	Annual product quality reviews	• System • Content • Applicability • Responsibilities • Trending procedures • Review period • Use of results for continuous improvement

APPENDIX II: ASSESSMENT SCHEDULE APPLIED DURING FIELD STUDIES

Based on defined assessment foci for the various key quality elements of WHO GMP, an assessment schedule had been prepared which was uniformly applied for the assessment of Kenyan pharmaceutical manufacturers regarding their existing level of compliance to WHO GMP. Each company was assessed for two full days. The assessment schedule is displayed in Table 5.

Table 5: Schedule for the assessment of Kenyan pharmaceutical manufacturers regarding their existing level of compliance to WHO GMP

<table>
<tr><td colspan="2">Day I</td></tr>
<tr><td rowspan="8">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 rowspan="2">Factory tour:
Warehouses
Receiving area and stores
Starting and packaging materials
Sampling and issuing
Production
Utilities
HVAC system
Water system
Compressed air system</td></tr>
<tr><td>Afternoon</td></tr>
</table>

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

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

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

Table 6: Indicators for score criteria for site

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

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

Table 7: Indicators for score criteria for QMS

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

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

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

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