Concept paper for discussion

A stepwise approach for pharmaceutical companies in developing countries to attain WHO GMP standards

This concept paper aims to provide a risk-based, phased approach for development of a country-specific, achievable roadmap towards WHO GMP for the manufacture of finished pharmaceutical products in low- and middle-income countries. The concept paper is based on the experience of the United Nations Industrial Development Organization (UNIDO) in developing and implementing national level GMP roadmaps. It describes the concept, the tools that have been developed and the process utilised for implementation. It is proposed for discussion on how policy makers and regulators can mitigate risk to public health during transition of an industry to GMP compliance based on a risk-based, phased roadmap.

Comments and suggestions on this paper are invited to facilitate further discussion. They should be sent to druginfo@who.int.

Introduction

Background
Adherence to Good Manufacturing Practices (GMP) is essential for consistent quality assurance of medicinal products and is important for ensuring their consistent safety and efficacy. However, due to the lack of financial, technical and human resource capacities, pharmaceutical manufacturers in developing countries are often overwhelmed by the vast array of GMP requirements and therefore fail to operate in line with such internationally acceptable standards. The situation is fuelled by the fact that regulatory authorities in many developing countries cannot meet the demands associated with internationally acceptable GMP standards. Of the more than 190 WHO Member States only “about 20% are known to have well developed drug regulation” whereas “30% either have no drug regulation in place or a very limited capacity that hardly functions” (1). As a result, pharmaceutical companies located in developing countries frequently feature operating environments and procedures that fall below standards that should ultimately be acceptable. Due to the lack of unified quality requirements, individual companies trying to improve their manufacturing standards are struggling to remain competitive in the low-priced market while many manufacturers are discouraged from making the necessary investments that are required to upgrade. According to WHO low- and middle-income countries bear the greatest burden of substandard products (2), whereby the rate of substandard...
products can even exceed 60% in particular countries for certain life-saving drugs such as anti-malarials (3). The use of substandard medicines can lead to harmful and even lethal consequences including therapeutic failure, drug resistance or toxicity.

Thus, there clearly exists an urgent need for improvement of existing manufacturing standards. However, there are significant challenges to raising standards. A central requirement to address the multitude of issues is the establishment of a stepwise technical pathway towards GMP compliance based on an assessment of the current situation within a country.

**Purpose**

This concept paper explains UNIDO’s approach to developing a country-specific, achievable roadmap towards internationally acceptable GMP standards, such as those issued by the World Health Organization (WHO). The paper points out the need for a risk-based, phased roadmap towards WHO GMP compliance and explains required steps and tools for its development.

The purpose of this document is to provide the technical aspects of developing a stepwise, phased, and risk-based approach for pharmaceutical manufacturers to reach full WHO GMP compliance. This roadmap shall set the path for the industry in individual countries to progress within a specified period of time to compliance with the internationally acceptable GMP standards defined by WHO.

The document also highlights the various benefits that such a GMP roadmap approach has for the pharmaceutical sector in developing countries. Finally, this paper provides an example of the successful application of the roadmap concept in a developing country as evidenced by the implementation of the Kenya GMP Roadmap (6).

This document should be read in conjunction with the respective WHO GMP guidelines mentioned in Footnote 1.

**Scope**

This document focuses on WHO GMP requirements for the manufacture of medicines in their finished dosage forms. Although the concept was initially developed for the manufacture of non-sterile dosage forms containing small molecular entities, the strategic approach presented in this paper can be applied to various GMP environments as long it is ensured that internationally recognized GMP guidelines are utilized as reference standard and that risks resulting from existing manufacturing practices are adequately mitigated during the progress of companies from existing practices to full compliance with GMP.

**GMP roadmap concept**

**Need for a risk-based, phased approach towards WHO GMP**

Observations from GMP inspections performed by WHO at manufacturers of medicinal products in developing countries revealed a high number of deviations from WHO GMP, including some critical deficiencies posing a potential risk of harm to patients (7). GMP compliance assessments conducted recently by UNIDO as part of the GMP roadmap work resulted in the observation of similar deficiencies, underlining the urgent need for improvement of existing manufacturing standards. For the majority of pharmaceutical manufacturers in developing countries the gap between WHO GMP requirements and current manufacturing practices is
substantial. Therefore, the transition from current manufacturing practices to full compliance with WHO GMP standards is a time-consuming process which cannot be achieved overnight. In order for the upgrading approach to be realistic and achievable, a stepwise, phased pathway with clearly defined milestones and targets at the end of each phase should be developed, guiding the pharmaceutical sector from the status quo to the targeted WHO GMP compliance.

While developing such an approach, it is essential to identify those areas of WHO GMP where companies are least compliant. These areas pose the biggest threat to the quality, safety and efficacy of the medicinal products manufactured and therefore have to be addressed with priority in order to avoid exposing patients to preventable risks.

In summary, this highlights that to ensure an achievable and hence realistic pathway towards full WHO GMP compliance the roadmap approach has to be

• risk-based, focusing first on those areas of WHO GMP with which least compliance exists and which are hence posing the highest risk to the quality, safety and efficacy of medicines manufactured; and
• structured in phases allowing a stepwise transition to full WHO GMP compliance with clearly defined targets at the end of each phase.

Steps for a risk-based, phased approach towards WHO GMP compliance in a specific country

Step 1: Baseline assessment of existing manufacturing practices
The baseline assessment is the starting point for the development process leading to a GMP roadmap. During the baseline assessment field studies are performed on a sample of pharmaceutical manufacturers which have not yet achieved full compliance with WHO GMP. Thereby it has to be ensured that the sample of pharmaceutical manufacturers selected for the baseline assessment is representative of the various levels of compliance with WHO GMP within a country.

WHO GMP is a highly suitable GMP reference standard as it is based on unified principles and practices agreed by the world’s leading regulatory agencies and hence receives wide international acceptance. Besides, many pharmaceutical manufacturers in developing countries strive to achieve compliance with WHO GMP as part of the requirements for having their products prequalified by WHO.

It is essential that this baseline assessment is well prepared and conducted thoroughly, as its results provide the basis for the specific design of the GMP roadmap. Therefore, unified tools have to be developed and applied equally to all pharmaceutical manufacturers participating in the baseline assessment in order to ensure transparency and consistency of obtained results. These tools include 1) the definition of key elements and focus areas during assessments; 2) preparation of an assessment schedule to be applied to all companies; and 3) the definition of rating of observations.

WHO GMP can be divided into 17 key areas which are called “key quality elements”, listed below.
1. Pharmaceutical Quality System
2. Utilities impacting Good Manufacturing Practices (GMP)
3. Sanitation and hygiene
4. Qualification and validation
5. Complaints
6. Product recalls
7. Contract production, analysis and other activities
8. Self-inspection, quality audits and suppliers’ audits and approval
9. Personnel
10. Training
11. Personal hygiene
12. Premises
13. Equipment
14. Materials
15. Documentation
16. Good practices in production
17. Good practices in quality control

For each of these key quality elements the assessment focus has to be defined. Based on the defined key quality elements and focus areas, an assessment schedule is prepared which is uniformly applied to all companies. In order to allow for a thorough assessment while at the same time avoiding too lengthy a time period for the field study, it is recommended that the assessment of each company takes two full days. Deficiencies of individual companies observed during the assessment are rated using a standard rating scheme of “critical”, “major”, “other”, as outlined for example in the compilation of EU “Community Procedures on Inspections and Exchange of Information” (8).

Step 2: Evaluation of assessment results and identification of common main technical challenges

In order to evaluate the level of compliance with WHO GMP and to identify the main technical challenges across the range of pharmaceutical companies within individual countries, two tools have been developed:

1. Identification of key quality elements affected by highest and lowest compliance with WHO GMP; and
2. Risk categorization of companies based on their compliance with WHO GMP.

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

Using the plain ratings of individual observations made during each company assessment would not be suitable to identify common main challenges across the pharmaceutical sector in a given country. Rather, a tool is required to compare individual companies in terms of their compliance with WHO GMP and to identify those key quality elements where highest and lowest compliance rates are observed. Therefore, a rating scheme has been developed that enables aggregation of individual observations related to a specific key quality element so as to reflect its composite compliance with WHO GMP requirements. The rating scheme comprises the following three levels:

- Compliance of a key quality element with WHO GMP is rated “acceptable” if no or only “other” (i.e. “minor”) deficiencies have been observed in areas related to this specific key quality element.
- Compliance of a key quality element with WHO GMP is rated “requires improvement” (short: “improve”) if only few “major” deficiencies (n ≤ 5) were observed in areas related to this specific key quality element.
- Compliance of a key quality element with WHO GMP is rated “inadequate” if at least one “critical” and/or a considerable number (n > 5) of “major” deficiencies are observed in the respective area or if the entire key quality element is not available at a company.

This rating key makes it possible to compare company performances and to identify those key quality elements for which highest and lowest compliance has been observed. In this way the main technical challenges for compliance can be identified. The rating key is a useful tool to evaluate particular weaknesses in compliance of pharmaceutical manufacturers within a country.

The described evaluation tool can also be used for trending of GMP compliance of companies and for monitoring their development towards full WHO GMP compliance throughout the implementation of the roadmap.
Tool 2: Risk categorization of companies based on their compliance with WHO GMP

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

The risk classification uses a matrix to categorize companies based on the two risk-indicating factors for GMP compliance: 1) Compliance of site with WHO GMP standards; and 2) Compliance of quality management system with WHO GMP standards.

A score of “1”, “2” or “3” is assigned to both the site and the quality management system to describe their respective degree of compliance with WHO GMP. A score of “3” represents high compliance-related risk whereas a score of “1” indicates low compliance-related risk.

A matrix is used for combining these two scores in order to generate an estimate of the overall compliance-related risk associated with a pharmaceutical manufacturer (Table 1). The resulting risk ratings are “A”, “B” and “C”, with a rating of “C” representing a high-risk company and a rating of “A” indicating a low risk company.

In order to increase the transparency and objectivity of the scores given for the compliance of site and QMS with WHO GMP, indicator criteria have been defined which are presented in Annex 1.

This risk categorization is a suitable tool for benchmarking GMP compliance of companies and can also be used in conjunction with “Tool 1” to monitor the companies’ progress in the upgrading process towards full WHO GMP compliance.

Additionally, the tools presented above can be utilized by individual pharmaceutical manufacturers in the context of a gap analysis and in order to prioritize and streamline corrective and preventive actions (CAPA).

Step 3: Design of a GMP roadmap based on evaluation results

Based on the evaluation outcomes a risk-based, phased GMP roadmap can be designed. Tool 1 identifies the key quality elements for which the most severe deficiencies versus WHO GMP exist and hence identifies the main technical challenges for the sector within the country which need to be addressed with highest priority. Tool 2 allows one to determine whether the main reason for

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**Figure 1: Interconnection between Site, QMS and GMP**

<table>
<thead>
<tr>
<th>Good manufacturing practice (GMP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site Physical entity mainly:</td>
</tr>
<tr>
<td>• Premises</td>
</tr>
<tr>
<td>• Utilities</td>
</tr>
<tr>
<td>• Equipment</td>
</tr>
<tr>
<td>Quality management system (QMS):</td>
</tr>
<tr>
<td>• Systems</td>
</tr>
<tr>
<td>• Procedures</td>
</tr>
</tbody>
</table>
low compliance with WHO GMP is caused by site- or QMS-related aspects of GMP, which helps to streamline the upgrading approach. Furthermore, this tool allows one to characterize the currently predominating level of compliance-related risk associated with pharmaceutical manufacturers within a country, and provides guidance in determining the number of phases needed to achieve full compliance with WHO GMP. If the predominantly existing compliance-related risk of the pharmaceutical companies in a country is rated as class “C” (i.e. predominance of high risk companies with inadequate manufacturing standards and procedures impairing production safety) at least 2 main phases will be needed to gradually improve from the existing level to full WHO GMP compliance: Phase I from level “C” to “B” will primarily focus on reducing the risk to production safety, Phase II from level “B” to “A” will aim to achieve full compliance with WHO GMP. In this context, it is well acknowledged that depending on the outcome of the evaluation it might be advisable to further divide the main phases into sub-phases. The content of those (sub-) phases will be primarily defined by the outcome of the compliance assessment of the key quality elements, with the first phase focusing particularly on those elements that show the most severe deviations from WHO GMP. Whether the first phase will put emphasis on site- or QMS-related GMP aspects will depend on the outcome of the company risk assessment to the extent that a distinct trend of compliance-related risk distribution between the two aspects is revealed.

As the individual phases of the GMP roadmap are defined according to the severity of deficiencies versus WHO GMP and the compliance-related risk observed at pharmaceutical manufacturers, the evaluation results are instrumental in realizing a stepwise, risk-based approach towards achievement of full WHO GMP compliance.
Benefits of a risk-based, phased roadmap towards WHO GMP

A risk-based, phased approach towards WHO GMP compliance has many benefits for the pharmaceutical sector of developing countries, including the following.

- The development of a risk-based, phased roadmap results in an achievable and scientifically sound pathway towards internationally acceptable GMP standards, which will eventually lead to a significant reduction of substandard medicines.
- A step-wise transition of pharmaceutical manufacturing practices towards a unified, internationally acceptable quality standard following clearly defined requirements, activities and milestones ensures the presence of a level playing field throughout the phases of the roadmap.
- The risk-based, phased roadmap ensures that all stakeholders have the same understanding of GMP throughout each of the transition phases,
  - demystifying requirements of WHO GMP and hence leading to an increased willingness to implement WHO GMP by the industry, and
  - increasing transparency during licensing procedures and regulatory GMP inspections and hence strengthening regulatory authorities.

A well-defined risk-based, phased roadmap will enable:

- already existing companies 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 to assure that all necessary elements and systems are taken into consideration and are in place before the actual launch of the company; and
- the regulatory authority to review licensing criteria for new and existing facilities, allowing existing companies to improve gradually until they are in line with WHO GMP requirements and ensuring that new companies comply with WHO GMP before their licensing.

Outlook on aligning the approach with other stakeholders’ activities

The risk-based, phased roadmap towards WHO GMP has to be anchored as a key component in a holistic approach for the development of the pharmaceutical manufacturing industry. In addition to a GMP roadmap many other components essential for the industrial development of the pharmaceutical sector in developing countries have to be taken into consideration. Those components, which include strengthening of the regulatory functions, access to affordable finance, development of incentive schemes, development of necessary human resources and securing distribution chains have to be addressed to enable sustainable high quality local production to be achieved through the GMP roadmap approach.

While the roadmap approach presented by UNIDO in this concept paper focuses on improving the quality of pharmaceutical manufacturing, other stakeholders, especially the Essential Medicines Department of WHO, are working on a risk assessment regarding the suitability of products for manufacture in companies according to their respective levels of compliance to WHO GMP. Both organizations have acknowledged the complementarities of the respective methodologies and have indicated willingness to incorporate them into a joint approach correlating the phases of the roadmap and the risk classification of pharmaceutical manufacturers with product manufacturing requirements.
A practical example of successful development of a risk-based, phased roadmap to WHO GMP compliance

The approach outlined above has been used to develop GMP roadmaps for Kenya and Ghana delineating the pathway from existing GMP compliance to full WHO GMP compliance. Country-specific roadmaps were devised taking into consideration the main technical challenges faced by manufacturers of medicinal products.

The development of the Kenya GMP Roadmap (6) is described here as a practical example for the successful development of a risk-based, phased GMP roadmap using the aforementioned approach.

The baseline assessment of existing manufacturing practices was performed at seven pharmaceutical companies that, while all falling short of full WHO GMP compliance, represented the different levels of manufacturers in the country. The scope of the baseline assessment was limited to the manufacture of small molecule, non-sterile medicinal products. The results shown below are anonymized and the sequence of the companies assessed is randomized, not allowing participants to be traced.

Using evaluation tool 1 the compliance of participating companies with key quality elements of WHO GMP was assessed. The results of this assessment, as shown in Figure 2, indicate that the companies’ compliance with WHO GMP was not rated acceptable for the majority of key quality elements.

Figure 2 also shows that seven key quality elements were associated with the lowest possible compliance rating (i.e. inadequate) in more than half of the participating companies. The elements listed below should be addressed with priority as they pose

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**Key quality element:**
- Utilities impacting GMP*
- Premises*
- Material handling*
- Good practices in quality control*
- Quality assurance**
- Sanitation and hygiene
- Qualification and validation
- Personal hygiene
- Complaints
- Product recalls
- Equipment
- Documentation
- Good practices in production
- Self-inspection and quality audits**
- Training
- Contract production and analysis**
- Personnel

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* Key quality elements written in red indicate those for which the highest number of companies showed least compliance.
** As the assessment had been performed before TRS 986, Annex 2 (5) became official, terms used for the key quality elements were based on TRS 961, Annex 3 (9), e.g. the term “Quality assurance” was used instead of “Pharmaceutical quality system”.

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![Figure 2: Compliance of participating companies with key quality elements of GMP](image-url)
the most severe risk to quality, safety and efficacy of the manufactured products:
• Quality assurance
• Utilities impacting Good Manufacturing Practices (GMP)
• Sanitation and hygiene
• Qualification and validation
• Premises
• Material handling
• Good practices in quality control

Evaluation tool 2 was used to categorize participating companies regarding their compliance with WHO GMP based on two risk-indicating factors, namely:
• Compliance of site with WHO GMP standards
• Compliance of quality management systems with WHO GMP standards

The results are displayed in Table 2.

### Table 2: Results of the risk categorization of companies based on their compliance with WHO GMP

<table>
<thead>
<tr>
<th>Company name</th>
<th>Risk score Site</th>
<th>Risk score QMS</th>
<th>Overall GMP rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Company 1</td>
<td>2</td>
<td>1</td>
<td>B</td>
</tr>
<tr>
<td>Company 2</td>
<td>2</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>Company 3</td>
<td>3</td>
<td>2</td>
<td>C</td>
</tr>
<tr>
<td>Company 4</td>
<td>3</td>
<td>2</td>
<td>C</td>
</tr>
<tr>
<td>Company 5</td>
<td>3</td>
<td>2</td>
<td>C</td>
</tr>
<tr>
<td>Company 6</td>
<td>3</td>
<td>2</td>
<td>C</td>
</tr>
<tr>
<td>Company 7</td>
<td>3</td>
<td>3</td>
<td>C</td>
</tr>
</tbody>
</table>

The risk assessment shows that out of the seven companies assessed only two achieved an overall GMP rating of “B” (medium risk company) whereas the remaining companies received an overall GMP rating of “C” (high risk company). The risk scores for compliance of the QMS with WHO GMP requirements ranged from “1” to “3”, the risk scores for compliance of the site with WHO GMP requirements ranged from “2” to “3”. This result underlines that the selection of companies was suitable for the assessment, as the selection criteria were to include companies representing different levels of GMP compliance (risk scores between “1” and “3”) while having not yet achieved full compliance with WHO GMP (no company with an overall GMP rating of “A”).

The risk assessment reveals that in general the scores for the site were higher than those related to the QMS. The usually higher risk associated with site was for almost all companies the main cause for downgrading the overall GMP compliance rating. This clearly indicates that particular guidance is needed regarding site-related GMP aspects and design requirements.

The following conclusions can be drawn from the assessment performed at pharmaceutical companies in Kenya and needed to be reflected in the design of the roadmap to WHO GMP compliance:
• Site-related GMP aspects need to be prioritized for improvement.
• Immediate measures are also required to reduce product-related risks caused by inadequacies of the QMS, with a special focus on those key quality elements with the lowest observed compliance ratings.

Taking into account the evaluation results, a risk-based, two-phased approach has been designed for the Kenya GMP Roadmap as shown in Figure 3.

Phase I focuses on the mitigation of risks impairing production safety by establishment of WHO GMP compliant sites and improvement of those QMS elements for which the majority of companies showed the most severe deficiencies versus WHO GMP (“QMS 1”). Using the results of the risk assessment, the majority of companies initially rated as “C” should reach a “B” rating at the end of Phase I as their sites (being a main contributory factor for their low GMP compliance rating) should then be in line with
WHO GMP requirements. 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 establishing a comprehensive, WHO GMP compliant quality management system (“QMS 2”) so that ultimately both structural (“site”) and organizational (“QMS”) measures for GMP compliance will be in line with WHO GMP. As the definition of the individual phases of the GMP roadmap is based on both the severity of deficiencies versus WHO GMP and the compliance-related risk observed at Kenyan pharmaceutical manufacturers, a stepwise, risk-based approach has been realized for the Kenyan roadmap towards achievement of full WHO GMP compliance. This technical roadmap provides for each of its phases a detailed breakdown of required actions and milestones for improvement of site-related and QMS-related GMP aspects. The structure of the Kenya GMP Roadmap is provided in Annex 2.

The roadmap has been complemented with an implementation plan embracing all facets required for successful implementation of the Kenyan roadmap towards compliance with WHO GMP requirements including definition of near- and mid-term requirements. The roadmap and implementation plan were agreed and endorsed by key stakeholders including representatives from industry and government (both policy-makers and regulators) during meetings in 2013 and 2014 and are part of the implementation of the Kenyan Pharmaceutical Sector Development Strategy.

The targeted timeline for implementation of the Kenya GMP Roadmap, as agreed amongst all stakeholders, is five years, whereby the first phase is targeted to take no longer than three years; and the second phase is targeted to be completed within two years.

Figure 3: Risk-based, phased approach of the Kenyan roadmap towards achievement of full WHO GMP compliance

<table>
<thead>
<tr>
<th>Overall GMP compliance rating</th>
<th>Phase focus and targeted outcomes</th>
<th>Phase number</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Site and Quality Management Systems in line with WHO GMP requirements</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>Improvement and implementation of those QMS with identified lower risk (QMS 2)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Site generally in line with WHO GMP requirements / QMS 1 in line with WHO GMP requirements</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>Improvement and implementation of those QMS for which majority of companies showed least compliance (QMS 1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Construction / modification of sites as per WHO GMP requirements</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Site and Quality Management Systems not in line with WHO GMP requirements</td>
<td></td>
</tr>
</tbody>
</table>
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.

In line with the implementation plan for the roadmap all Kenyan manufacturers of finished pharmaceutical products were assessed by internationally experienced GMP inspectors in conjunction with inspectors from the Pharmacy and Poisons Board in 2015. The outcome of the gap analysis project confirmed observations, conclusions and prioritizations made based on the baseline assessment for the development of the GMP Roadmap and hence verified the adequacy of the approach and the aforementioned tools used for the development of the GMP roadmap.

Conclusion
This document summarizes a methodology to develop a pathway for pharmaceutical manufacturers in developing countries to move towards WHO GMP standards. In order to be manageable and scientifically sound, the GMP roadmap should be risk-based and structured into phases. The concept has been successfully applied in Kenya and Ghana where country-specific GMP roadmaps have been developed in consultation with key domestic stakeholders including the pharmaceutical industry, regulators and relevant governmental departments. Assessments of all Kenyan manufacturers of finished pharmaceutical products by internationally experienced GMP inspectors in conjunction with inspectors from the Pharmacy and Poisons Board confirmed the observations, conclusions and prioritizations made based on the baseline assessment for the development of the Kenya GMP Roadmap and hence verified adequacy of the approach and the tools used for development of the GMP roadmap.

References
7 Thrussell I. Examples of critical and major observations from GMP inspections of Manufacturing, QC and Contract Research Organisations. Presented at the UNICEF Pharmaceutical Supplier Meeting 2012 on 26 September 2012.
The Kenyan roadmap towards achievement of full WHO GMP compliance
Source: (6)

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

**Indicators for score criteria for site**

<table>
<thead>
<tr>
<th>Prerequisite</th>
<th>Rating</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premises</td>
<td></td>
<td>Premises are designed to be suitable for pharmaceutical manufacturing</td>
<td>Premises show significant deficiencies from WHO GMP but do not impair production safety</td>
<td>Premises are unsuitable for pharmaceutical manufacturing → Production safety impaired</td>
</tr>
<tr>
<td>Utility</td>
<td></td>
<td>Utilities which have direct product contact (e.g. water, air handling, compressed dried air) are in place as required, suitable and effective/ functioning</td>
<td>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</td>
<td>Utilities which have direct product contact (e.g. water, air handling, compressed dried air) are not available although required, or available utilities are unsuitable</td>
</tr>
<tr>
<td>Equipment</td>
<td></td>
<td>Equipment for all manufacturing steps and quality controls are suitable to perform the operation and functioning</td>
<td>Equipment for at least critical manufacturing steps and quality controls are in place and suitable to perform the operation and functioning</td>
<td>Equipment for critical manufacturing steps and quality controls are not available or not functioning</td>
</tr>
</tbody>
</table>

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

**Indicators for score criteria for QMS**

<table>
<thead>
<tr>
<th>Prerequisite</th>
<th>Rating</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMP documentation and procedures</td>
<td></td>
<td>A systematic holistic approach towards GMP documentation is in place; procedures performed are adequate and based on a documented system</td>
<td>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</td>
<td>No GMP documentation is in place; procedures are totally inadequate</td>
</tr>
<tr>
<td>Calibration/ qualification/ validation</td>
<td></td>
<td>A systematic approach based on master documents, schedules, protocols and reports is in place</td>
<td>Checks for performance of critical equipment, instruments and methods done but not to an extent required and/or not based on a systematic approach</td>
<td>No calibration, qualification, validation are performed</td>
</tr>
<tr>
<td>Preventive maintenance</td>
<td></td>
<td>Comprehensive preventive maintenance procedures based on a systematic approach are in place.</td>
<td>Preventive maintenance for critical systems is performed but no systematic approach including schedules, protocols, reports/logs is in place</td>
<td>No preventive maintenance is performed.</td>
</tr>
<tr>
<td>Sanitation</td>
<td></td>
<td>Cleaning is adequate; a systematic approach to cleaning consisting of validation, cleaning schedules, logs is in place</td>
<td>No signs of inadequate cleaning are observed, but no systematic approach to cleaning including cleaning validation, schedules, logs is in place</td>
<td>Evidence of widespread accumulation of residues/ extraneous matter exists; evidence of gross infestation is observed</td>
</tr>
<tr>
<td>Material handling</td>
<td></td>
<td>Documented procedures for all types of material handling are in place in line with pharmacopoeia/ international guidelines</td>
<td>Testing of materials/products is performed but not to the extent 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</td>
<td>No testing of materials/products is performed. Procedures for receipt, sampling, storage, manufacturing and distribution are inadequate; no GMP documentation is in place</td>
</tr>
</tbody>
</table>
### Indicators for score criteria for QMS (continued)

<table>
<thead>
<tr>
<th>Prerequisite</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Personnel/training</strong></td>
<td>Personnel has the right qualification, experience and knowledge to perform duties assigned, training program is in place</td>
<td>Personnel has the right qualification and knowledge to perform duties assigned, but no training program is in place</td>
<td>Personnel does not have the right qualification, knowledge and experience to perform the duties assigned</td>
</tr>
</tbody>
</table>

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

#### Annex 2: Exemplary structure of the Kenya GMP Roadmap

**Start:** Site and quality management systems not in compliance with WHO GMP requirements

<table>
<thead>
<tr>
<th>Section 1.1: Phase I, Site</th>
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</thead>
<tbody>
<tr>
<td><strong>Phase/Ref. No.</strong></td>
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<tr>
<td>1.1.1 Premises</td>
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<tr>
<td><strong>End of section: Phase I, Site</strong></td>
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</tbody>
</table>

**Site compliant with WHO GMP, but quality management systems (QMS) not in line with WHO GMP**

<table>
<thead>
<tr>
<th>Section 1.2: Phase I, QMS</th>
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<tbody>
<tr>
<td><strong>Phase/Ref. No.</strong></td>
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<tr>
<td>1.2.1 Quality assurance</td>
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<td><strong>End of section: Phase I, QMS</strong></td>
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</tbody>
</table>

**Note:** During the improvement of site and QMS at already existing pharmaceutical manufacturers towards WHO GMP, activities outlined in Sections 1.1 and 1.2 should be conducted concurrently.

**Site and QMS identified as main technical challenges in Kenya compliant with WHO GMP**

<table>
<thead>
<tr>
<th>Section 2: Phase II</th>
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<tbody>
<tr>
<td><strong>Phase/Ref. No.</strong></td>
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<tr>
<td>2.1 Complaints</td>
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<td><strong>End of section: Phase II</strong></td>
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**Completion:** Site and QMS in compliance with WHO GMP