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White Paper on UNIDO's GMP Roadmap Concept

Design of a Stepwise Approach
for the Pharmaceutical Industry in Developing Countries
to Comply with WHO GMP



UNITED NATIONS
INDUSTRIAL DEVELOPMENT ORGANIZATION

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

2015



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INDUSTRIAL DEVELOPMENT ORGANIZATION

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Executive Summary

A high number of substandard medicinal products are causing severe health impacts on patients, especially in developing countries. Too frequently, cases of people being severely affected or even dying due to the consumption of sub-standard medicines occur. Significant reasons for the presence of such products are inadequate adherence to and enforcement of unified, internationally acceptable standards for Good Manufacturing Practices (GMP).

This white 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 document points out the need for a risk-based, phased roadmap towards WHO GMP compliance and explains required steps and tools for its development. The recommended development process involves consultation with key stakeholders in the country concerned, and can be outlined as follows:

- 1) Collecting baseline data on existing manufacturing practices
- 2) Evaluation of gathered information and identification of the main common technical challenges
- 3) Design of a GMP roadmap based on the evaluation results

The white paper also highlights the various benefits of a risk-based, phased GMP roadmap for the pharmaceutical sector in developing countries and describes the prospects of aligning the UNIDO approach with other stakeholders' activities in the future. Finally, the document outlines an example for the successful application of the roadmap concept in a developing country as evidenced by the implementation of the Kenya GMP Roadmap.

A. GMP Roadmap Concept

The Menace of Substandard Medicines in Developing Countries

Adherence to Good Manufacturing Practices (GMP) is essential for consistent quality assurance of medicinal products and also helps to ensure their 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 are unable 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 the enforcement of 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 to make the necessary investments that are required to upgrade. WHO estimates

that up to 25% of medicines consumed in developing countries are substandard (2), and for certain life-saving drugs such as anti-malarials the rate of substandard products can even exceed 60% in particular countries (3). The use of substandard medicines can lead to harmful and even lethal consequences including therapeutic failure, drug resistance or toxicity.

Thus, there is clearly an urgent need for improvement of existing manufacturing standards. But due to their lack of capacities many developing countries are facing huge challenges to raise their existing manufacturing standards to internationally acceptable GMP.

UNIDO's Approach to Improve Pharmaceutical Manufacturing Standards

As part of an ongoing global advisory and capacity-building project to strengthen the local production of essential generic medicines in developing countries, the United Nations Industrial Development Organization (UNIDO) helps devise strategies for the development of a commercially viable pharmaceutical sector that adopts manufacturing practices at internationally acceptable quality levels. A key component of UNIDO's approach is a roadmap that sets 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 the WHO¹.

This white paper focuses on the technical aspects of developing an achievable, country-specific roadmap that delineates a stepwise, phased, and risk-based approach for pharmaceutical manufacturers to reach full WHO GMP compliance.

Why is a risk-based, phased approach essential for the development of an achievable roadmap?

Observations from GMP inspections performed by WHO at manufacturers of medicinal products in developing countries revealed a high number of severe deviations from WHO GMP with some of those shortcomings being the reason for fatal incidents (4). 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 enormous. Therefore, the transition from current manufacturing practices to full compliance with WHO GMP standards is a time-consuming process which cannot be achieved "over-night". 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.

¹ The GMP standard referred to in this document is as outlined in (6) and subsequently updated through the WHO Technical Report Series (TRS). While TRS 961, Annex 3 (7) was current at the time of the roadmap development as described in this paper, the most recent reference version is TRS 986, Annex 2 (8).

While developing such a phased 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 risk.

In summary, this highlights that for ensuring 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 imposing the highest risk on quality, safety and efficacy of medicines manufactured;
- structured in phases allowing a stepwise transition to full WHO GMP compliance with clearly defined targets at the end of each phase.

What are the steps to develop a risk-based, phased approach to WHO GMP compliance for a specific country?

In order to develop a risk-based, phased roadmap to WHO GMP compliance for a specific country the baseline of the existing manufacturing practices across the range of companies needs to be established. This is done by performing field studies of the current level of compliance of pharmaceutical manufacturers with WHO GMP standards. The information gathered during the field studies is evaluated, and the main technical challenges commonly faced by the companies within a country are identified. Based on the study results obtained a phased, risk-based approach to compliance with WHO GMP can then be designed.

Thus, the development of a risk-based, phased approach to WHO GMP compliance is a 3-step process that can be summarized as follows:

- 1) Collecting baseline data on existing manufacturing practices
- 2) Evaluation of gathered information and identification of the main common technical challenges
- 3) Design of a GMP roadmap based on the evaluation results

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 of the pharmaceutical manufacturers' level of compliance with WHO GMP are performed 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.

The aforementioned tools include:

- 1) Definition of key elements and focus areas during assessments
- 2) Preparation of an assessment schedule to be applied to all companies
- 3) Definition of rating of observations

WHO GMP can be divided into 17 key areas which are called "key quality elements":

- | | |
|---|---------------------------------------|
| 1. Quality assurance | 9. Personnel |
| 2. Utilities impacting Good Manufacturing Practices (GMP) | 10. Training |
| 3. Sanitation and hygiene | 11. Personal hygiene |
| 4. Qualification and validation | 12. Premises |
| 5. Complaints | 13. Equipment |
| 6. Product recalls | 14. Materials |
| 7. Contract production and analysis | 15. Documentation |
| 8. Self-inspection and quality audits | 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" (5). The selection of pharmaceutical companies to be assessed should include manufacturers at different levels of compliance with WHO GMP.

Step 2: Evaluation of assessment results and identification of 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
- 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 ($n \leq 5$) 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.

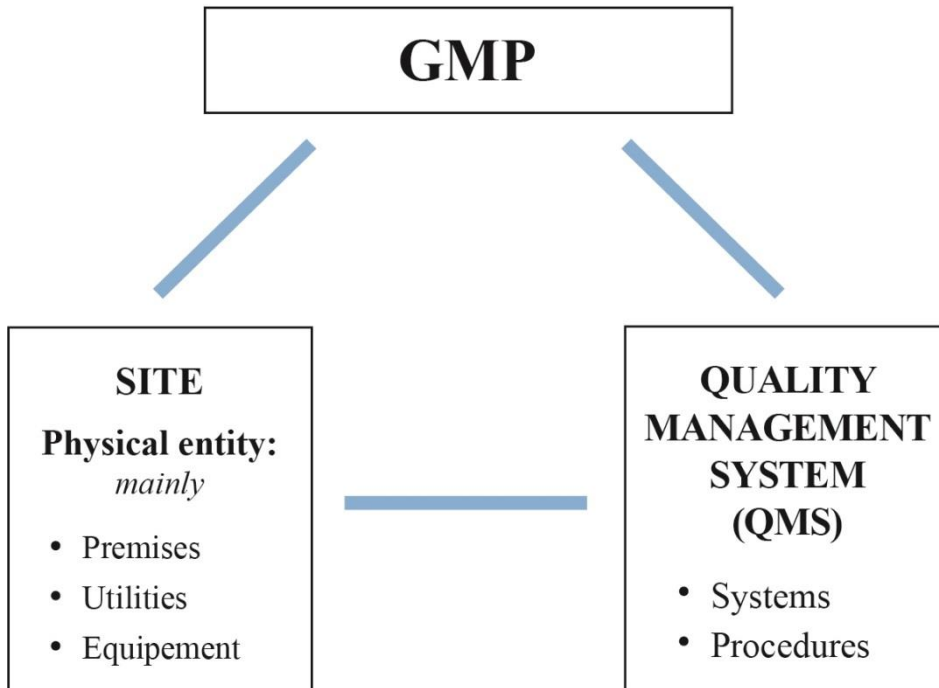
This rating key makes it possible to compare company performances and to identify those key quality elements to which highest and lowest compliance has been observed. Hence, main technical challenges for compliance can be identified. The rating key is a useful tool to evaluate particular weaknesses in 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 white 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.

Figure 1: Interconnection between Site, QMS and GMP.



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
- 2) Compliance of quality management system with WHO GMP standards

A score of “1”, “2” or “3” is assigned to both site and 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, displayed as table 1 on the following page, is used for combining these two scores in order to generate an estimate of the overall compliance-related risk associated with a pharmaceutical manufacturer. 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.

Table 1: Risk matrix for the 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

It should be noted that in order to increase transparency and objectivity of the scores given for the compliance of site and QMS with WHO GMP, indicator criteria have been defined though they are not included in this white paper.

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 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 of 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 severest 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. In section B further below, the successful development of a risk-based, phased roadmap utilizing the above approach for Kenya is provided as an example.

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. Such benefits include:

- 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,
 - 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;
- the regulatory authority to review licensing criteria for new and existing facilities in order to improve them gradually until they are in line with WHO GMP requirements.

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 including strengthening of the regulator, access to affordable finance, development of incentive schemes, development of necessary human resources and securing distribution chains have to be aligned with the requirements of the GMP roadmap.

While the roadmap approach presented by UNIDO in this white paper focuses on improving the quality of pharmaceutical manufacturing, other stakeholders, especially the Essential Medicines Department of the 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.

B. A practical example for successful development of a risk-based, phased roadmap to WHO GMP compliance

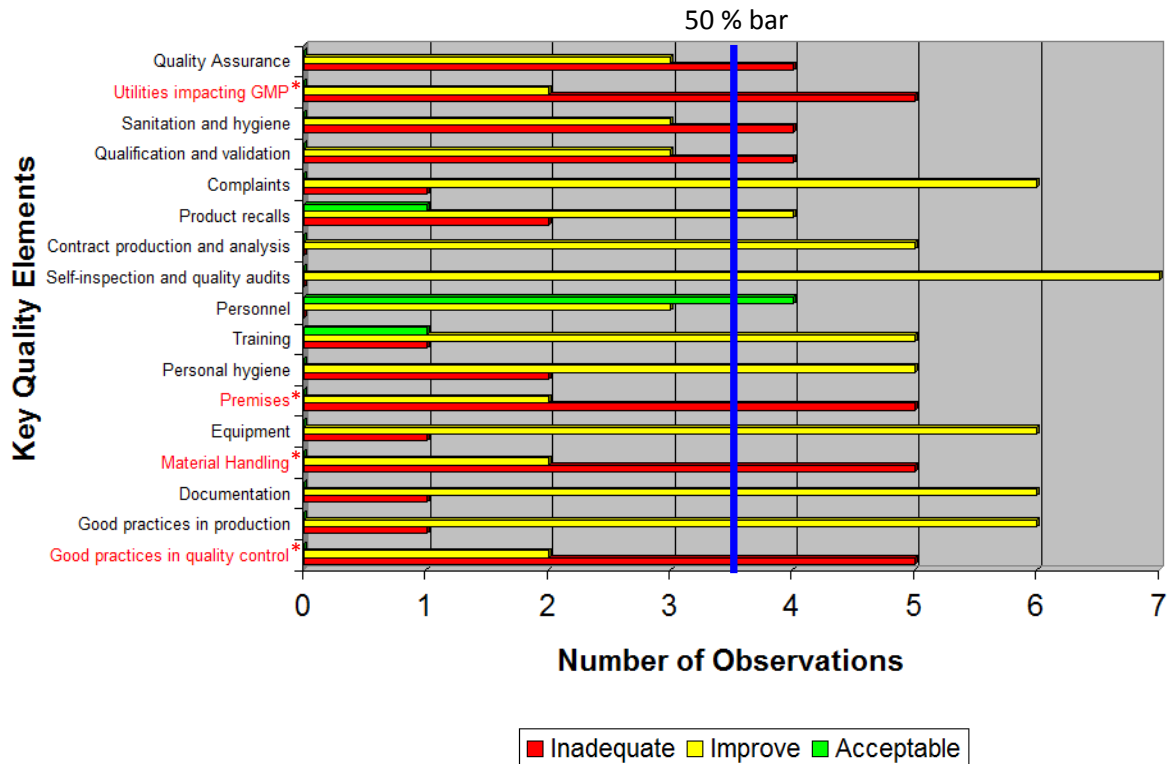
The approach outlined above has been used to develop a roadmap for Kenya delineating the pathway from existing GMP compliance to full WHO GMP compliance. A country-specific roadmap was devised taking into consideration the main technical challenges faced by manufacturers of medicinal products in Kenya. The scope of this roadmap was limited to the manufacture of small molecule non-sterile medicinal products.

The baseline assessment of existing manufacturing practices was performed at 7 pharmaceutical companies that, while all falling short of full WHO GMP compliance, represented the different levels of manufacturers in the country. The results displayed in the following 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 has not been rated acceptable for the majority of key quality elements. Figure 2 also shows that 7 key quality elements are associated with the lowest possible compliance rating (i.e. inadequate) in more than half of the participating companies. These elements as listed below should be addressed with priority as they pose 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

Figure 2: Overview of compliance of participating companies with individual key quality elements of GMP.



*Key quality elements written in red indicate those for which the highest number of companies has shown least compliance.

Evaluation tool 2 was used to risk 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.

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 risk assessment shows that out of the seven companies assessed only two companies 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 QMS with WHO GMP requirements ranged from “1” to “3”, the risk scores for compliance of 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 site were higher than those related to 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 need 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 rates.

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.

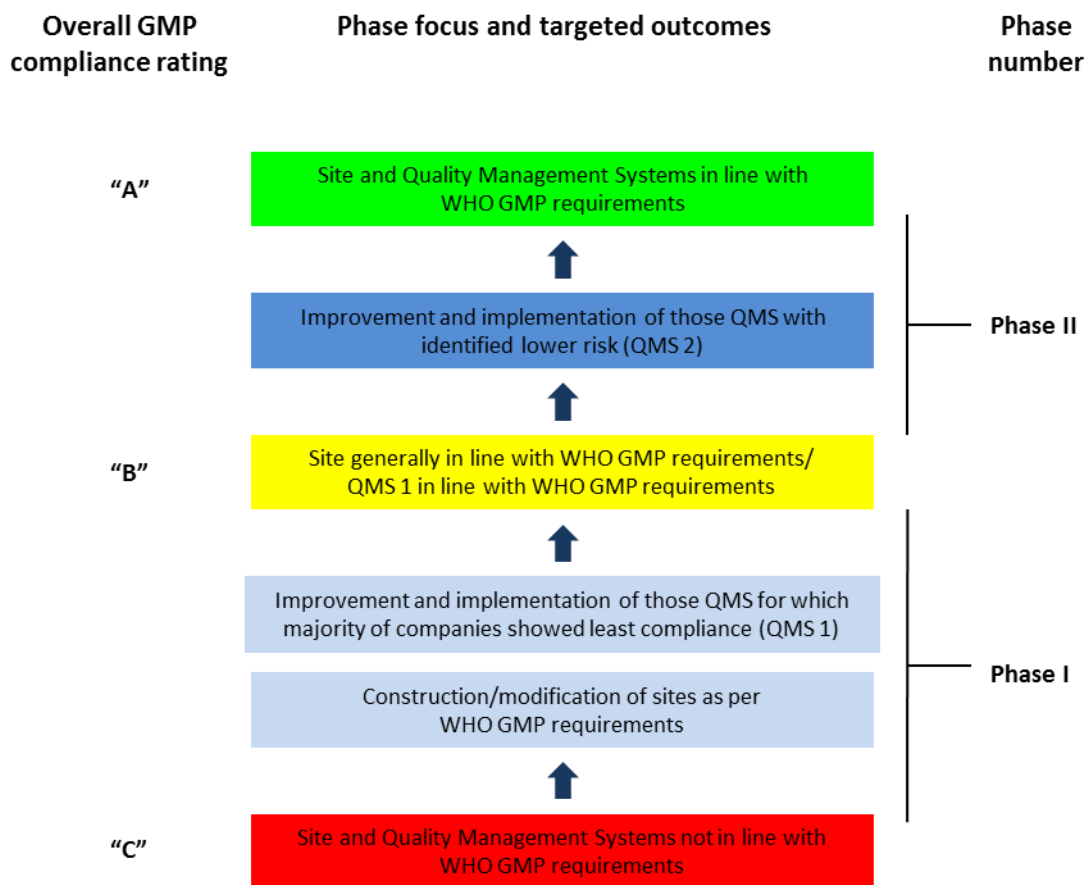
Phase I focuses on the mitigation of risks impairing production safety by establishment of WHO GMP compliant sites and improvement of those QMS elements for which the majority of companies showed the most severe deficiencies versus WHO GMP. Using the results of the risk assessment, the majority of companies 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 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 GMP aspects, AND
- for improvement of QMS related GMP aspects.

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



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. Roadmap and implementation plan were agreed and endorsed by key stakeholders including representatives from industry and government (both policymakers and regulators) during meetings in 2013 and 2014.

C. Conclusion

This white paper summarises a methodology to develop a pathway for pharmaceutical manufacturers in developing countries to move towards WHO GMP production standards. In order to be manageable and scientifically sound, the GMP roadmap should be risk-based and structured into phases. The concept, as presented, is receiving wide recognition in the international development and global public health arenas. It has been successfully applied in Kenya where a country-specific GMP roadmap has been developed in consultation with key domestic stakeholders including the pharmaceutical industry, regulators and relevant governmental departments.

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