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Good Manufacturing Practices in the Kenyan Pharmaceutical Industry and Impact of Facility Upgrading on Domestic and International Sales

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Good Manufacturing Practice is the main regulatory standard for ensuring pharmaceutical quality. Manufacturers are required to comply with this standard to warrant medicines which do not pose risk to consumers. The aim of this study was to assess compliance of Kenyan pharmaceutical industry with Good Manufacturing Practices and to determine the impact of facility upgrading on domestic and international sales. Information on key quality elements was collected from 16 manufacturers using a structured questionnaire. Data on domestic and export sales for two upgraded facilities was evaluated for the period, 2010 to 2014. Compliance with Good Manufacturing Practices varied amongst the facilities; all had local accreditation, 11 were accredited by Drug Authorities in East Africa region and 3 held international certification. Domestic sales for two facilities declined after upgradation and international sales increased fivefold for the facility accorded international accreditation. Upgrading of facilities improved international trade but negatively impacted domestic sales.

KEY WORDS: Compliance, manufacturing, pharmaceutical, sales, upgrading.

INTRODUCTION

Good Manufacturing Practices (GMP) in the pharmaceutical industry is that part of quality management which ensures that products are consistently produced and controlled to the quality standard appropriate to their intended use and as required by marketing authorization, clinical trial authorization or product specification [1, 2]. Testing for compliance with specifications does not guarantee that a product will have the expected quality [3]. Pharmaceutical manufacturers are required to comply with GMP regulations with emphasis on quality assurance within the production process to ensure quality products which do not pose any risk to the consumer are made [4-6]. The GMP guidelines that are widely applied in the pharmaceutical industry are from the European Medicines Agency, the United States Food and Drug Administration, the World Health Organization (WHO) and the International Conference on Harmonization [7]. The WHO guidelines contain 17 quality elements namely; quality assurance, utilities impacting on GMP, sanitation and hygiene, qualification and validation, complaints, product recalls, contract production and analysis, self-inspection, personnel, training, personal hygiene, premises, equipment, materials, documentation, good practices in

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production and in quality control. Enforcement of GMP lies on drug regulatory authorities (DRAs) in individual countries.

In 2014, the Kenyan pharmaceutical manufacturing industry consisted of 24 licensed companies engaged in secondary and tertiary production of medicines for human use. Six facilities produced veterinary products. The Pharmacy and Poisons Board (PPB) of Kenya regulates the manufacturing operations and performs regular inspections of pharmaceutical manufacturers to ensure compliance with GMP standard. Three manufacturers received the European Pharmaceutical Inspection Cooperation Scheme certification in 2007, and one facility was accorded WHO prequalification in 2011 [8].

In its endeavor to improve GMP in the local pharmaceutical industry, the PPB has partnered with United Nations International Development Organization (UNIDO), the Ministry of Industry, pharmaceutical manufacturers and other stakeholders to establish a GMP Roadmap which is a stepwise approach towards attaining compliance with WHO-GMP standard [9]. The roadmap was launched in December 2014, and is projected to be implemented within 5 years. Compliance with GMP is capital intensive as it demands appropriately designed premises that are fitted with quality impacting utilities, production machinery, quality systems and technical expertise. Upgrading of manufacturing facilities may have an impact on the domestic market share and access to essential medicines through local production in developing countries where the market is sensitive to price. The aim of this study was to assess compliance of pharmaceutical manufacturing facilities in Kenya with Good Manufacturing Practices and to determine the impact of facility upgrading on domestic and international sales.

EXPERIMENTAL

Data Collection

A survey was conducted on compliance of Kenyan pharmaceutical manufacturing industry with GMP quality standard and on sales turnover for two upgraded facilities. Data was collected using a comprehensive structured questionnaire which was sent to 24 manufacturers of human pharmaceutical products. The questionnaire was administered to Quality Heads, the persons who are accountable for quality assurance at the manufacturing facilities. The data collection process entailed making telephone calls, sending electronic mails and a visit to each facility. Information was obtained on GMP accreditation status of facilities (local, regional and international) and compliance of facilities with key GMP quality elements that require vast capital investment namely; premises, utilities impacting GMP, practices in quality control, research and development (R&D) and personnel. Data on sales turnover for two companies that had upgraded their manufacturing facilities, 'F' having achieved local accreditation and 'N' with both local and international accreditation was collected for a period of 5 years (2010-2014).

Data analysis

Assessment of compliance with GMP standards was based on global rating of GMP audit findings in the pharmaceutical industry [10-12]. The rating depended on risk of the finding (deficiencies) on quality, considering the nature of the deviations. All parameters were rated on a scale of one to four (1-4) as; 1(*unsatisfactory* - critical observations, unsuitable premises), 2(*poor* - critical and major deficiencies), 3*(satisfactory* - few major and minor deficiencies), 4(*good* - minor deficiencies). A mean score of more than 2 was construed as GMP compliance and that of 2 or less as non-compliance. The findings on GMP

compliance were affirmed by a PPB of Kenya inspectorate representative. Workforce in various departments in this industry and their qualifications were evaluated. Domestic, export and international (local and export) sales for the two companies, F and N were analyzed to determine any trend in the market share before and after facility upgrading.

RESULTS

Respondent manufacturers

Sixteen of the 24 manufacturers of pharmaceutical products for human use, comprising a research institute that makes rapid diagnostic kits, one manufacturer of sterile products and 14 non-sterile manufacturers responded to the questionnaire on GMP practices in the local pharmaceutical industry. The respondents included the 8 large pharmaceutical manufacturers in Kenya. Solid, semisolid and liquid dosage forms were manufactured at the sites.

The GMP accreditation status of manufacturing facilities

All the manufacturers assessed had GMP accreditation by the PPB of Kenya and 11 facilities had been approved by various DRAs in the East Africa region. Three manufacturers received the European Pharmaceutical Inspection Cooperation Scheme (PICS) certification in 2007. One of these manufacturers was further accorded WHO prequalification for the antiretroviral (ARV) zidovudine-lamivudine in 2011 and had submitted a second dossier for evaluation. One other company was in the final stages of WHO-GMP prequalification process for an ARV drug at the time of this study.

Manufacturing premises and utilities

Table 1 presents the overall GMP compliance rating of the companies that were assessed. Nine of the sixteen respondent facilities were appropriately designed to allow unidirectional flow of personnel and materials. Production areas were ventilated through air handling units. Nine facilities had installed terminal high efficiency particulate air (HEPA) filters in production areas to prevent cross-contamination of products. Six facilities utilized high capacity blowers to propel air through coarse filters (G4 and F8) into production areas. Water for pharmaceutical use, BP standard was used in production processes at all 16 facilities. Reverse osmosis and/or deionization were used to purify water. Eight facilities had a circulating loop system which provided good control of viable particulate matter.

Quality control

The quality control (QC) department at all 16 manufacturers was adequately equipped to perform tests for most of the raw materials and finished products. Some manufacturers could not carry out analysis of volatile oils due to lack of a gas chromatograph and approval of these materials were based on supplier certificate of analysis. Specifications were available for materials tested. The head of QC was responsible for approval of both raw materials and finished products. Most of the QC analysts were diploma or Bachelor of Science (B.Sc.) graduates. The department was headed by B.Sc. graduates who were proficient in pharmaceutical analysis.

Table 1: Good Manufacturing Practice compliance rating of firms in the local industry

Company code	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
Overall rating	3	2	2	3	2	3	3	3	2	2	2	3	2	4	3	4

Research and development

The local pharmaceutical industry was engaged in generic medicine production. Majority of manufacturers performed limited R&D activities. Three manufacturers; a research institution (P in Table 1) that produced rapid diagnostic kits and two other manufacturers had nascent R&D departments. Nine manufacturers were in the processes of setting up this unit, whereas four manufacturers carried out formulation activities either in QC or production areas. The R&D activities focused mainly on formulation and product quality improvement studies. Two companies had ventured into collaborations with multinationals in order to improve their technical capacity. Between 2004 and 2006, the two companies utilized trade related aspects of intellectual property rights (TRIPS) flexibilities to obtain voluntary licenses from patent holders for production of antiretroviral drugs [13].

Personnel

The workforce at the 16 respondent manufacturers in 2014 was 2,798, consisting of persons of different qualifications and skills. Most of the skilled workers had at least diploma qualification, specializing in pharmacy, chemistry, biochemistry, microbiology and engineering. Among these employees, 2 were doctorate (pharmaceutical sciences) holders and 33 were pharmacists. One company had engaged 5 pharmacists, two companies had 4 pharmacists each, two had 3, four had 2, six had 1, and one facility had no pharmacist. The workers were deployed in production, quality assurance, quality control, maintenance, regulatory, research and development and their distribution is as shown in Figure 1.

Majority of the employees worked in production department. The compliance section (quality assurance (QA), quality control and regulatory) in most of the facilities had adequate number of staff with appropriate qualifications, mainly diploma or B.Sc. holders and pharmacists. The R&D section had the least workforce (1%) and in 2014, the industry had employed 27 persons in this department comprising 5 pharmacists, 7 B.Sc. graduates, 3 diploma holders and 12 machine operators with basic school education.

Personnel employed in production, quality assurance, quality control and regulatory affairs departments were proficient in basic knowledge (qualifications) but deficient in practical skills, and these were mostly acquired through ‘on the job’ training. Personnel with know-how and skills in specialized areas such as product development, formulation design and pharmaceutical engineers were inadequate. The ‘others’ category were personnel deployed in administration, sales and marketing departments that form an integral part of product manufacturing cycle.

Overall GMP compliance rating of facilities

Table 1 demonstrates that compliance with GMP standard varied among the facilities in the Kenyan pharmaceutical industry. Premises and air handling units were satisfactory at 9 facilities. All facilities had a water purification system capable of producing suitable water for pharmaceutical use. Quality control unit, personnel capacity and R&D department were satisfactory at 14, 6 and 2 facilities, respectively. The overall rating of 9 facilities was satisfactory. The whole industry has now embraced the Kenya GMP Roadmap which aims at improving the local industry to achieve international GMP standards.

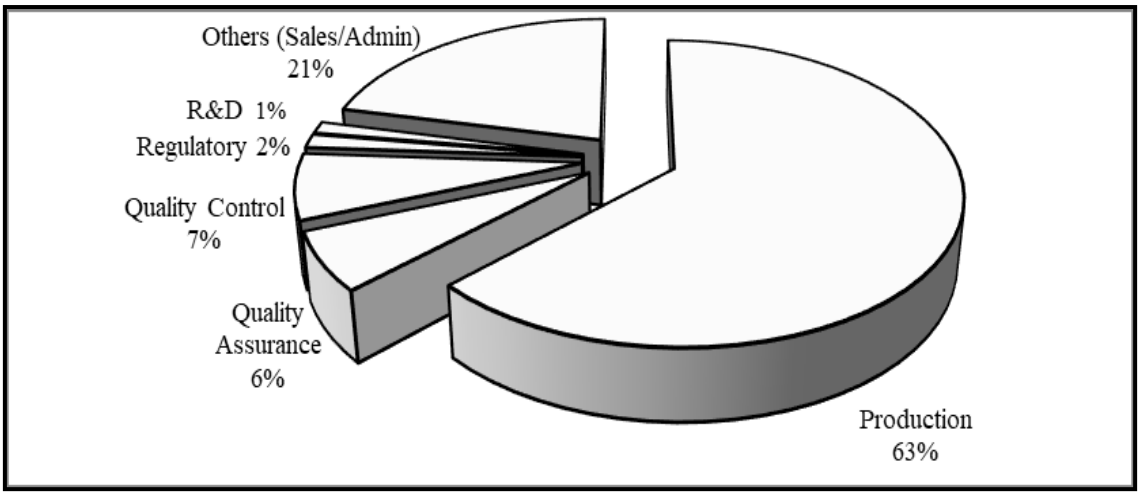

Figure 1: Deployment of workers in the Kenyan pharmaceutical industry.

Impact of facility upgrading on local, export and international tender sales

The main clients for the local pharmaceutical industry were public procurement agencies and distributors within Kenya and the Common Market for Eastern and Southern Africa region. Procurement of medicines by public agencies in Kenya was through a tendering process, normally awarded to the bidder with the lowest quoted price. Figure 2 shows the local and export sales for two companies, F and N that upgraded their facilities. Manufacturer F was disqualified from participation in international tenders due its non-prequalification status. Local sales for both facilities decreased after facility upgrading. However, sales through international tender awards, mainly from United Nations International Children's Emergency Fund (UNICEF) for company N increased fivefold from 2012 to 2014. In 2014, manufacturer N sold 35 % to local market, 15 % to export market and 50 % to international tenders. By 2014, the sales to a local public procurement agency had decreased by 50 % but the overall sales increased by 93.5 % since 2011.

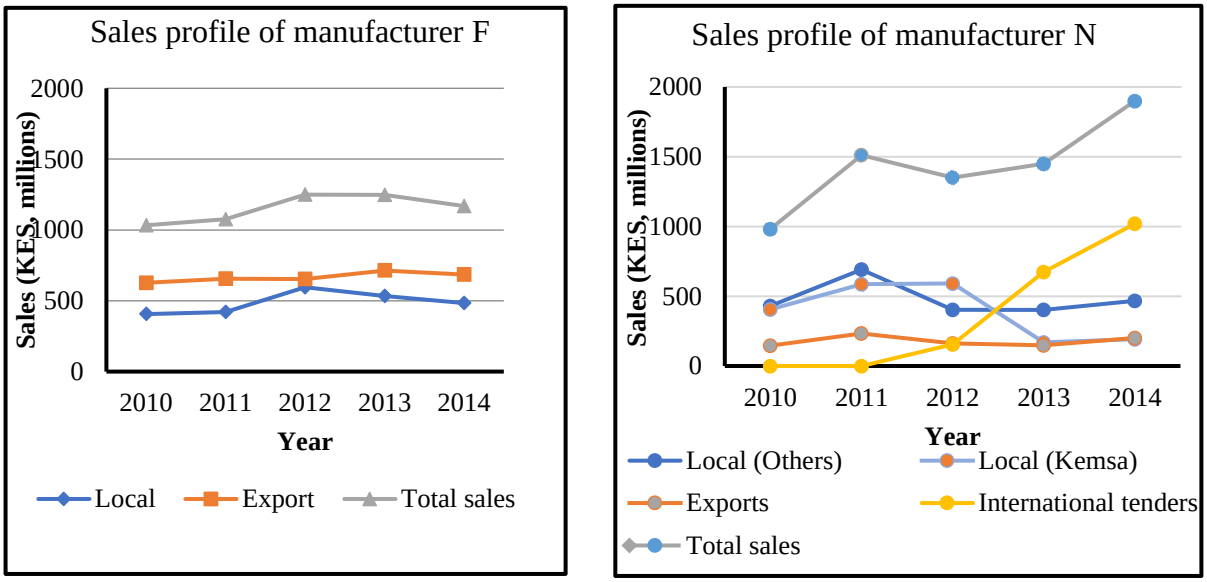

Figure 2: Sales profile of manufacturers F and N.

DISCUSSION

Compliance of Kenyan pharmaceutical industry with GMP standards

Adherence to GMP is a prerequisite for marketing authorization of pharmaceutical products. All the manufacturers in this study were GMP certified by the PPB of Kenya and 11 of these had attained regional accreditation to market products in the vast Eastern and Southern Africa countries. Compliance with GMP standard differed among facilities in this industry and the variance could be attributed to the manufacturer's target market and access to investment capital. Facilities which were pursuing export market and accreditation from stringent DRAs had upgraded their facilities to comply with both local and international GMP standards. Many developing countries including Pakistan, Tanzania and Zambia face challenges of adherence to international GMP standards mainly due to lack of investment capital which is required for upgrading facilities to comply with GMP concepts which are frequently revised making the standards more stringent [14-18].

The workforce at the 16 manufacturers was 2,798 accounting for 67 % of the documented 4,170 employees in this sector in 2014 [19]. The Deficiency of personnel with practical skills and experts in specialized fields such as pharmaceutical engineering is being addressed through contracted sourcing of specialists mainly from India. The PPB together with international partners such as UNIDO and the Federation of East African Pharmaceutical Manufacturers (FEAPM) are assisting in development of human capacity by providing specific GMP and QA trainings to personnel in the local industry. The satisfactory QC and QA sections at most facilities is an indication that production processes in this industry are under control, defects are identified and the quality of products manufactured is assured.

The Kenyan pharmaceutical industry is engaged mainly in manufacture of generic drugs and hardly in generation of new products through innovation. The main goal of R&D in pharmaceutical industry is to develop quality products that are appropriately designed and are fit for their intended use. The limited R&D activities in this industry may be attributed to inadequacies of technology, research scientists and investment capital. The high cost of developing a new drug (estimated as US$1.5 billion) compounded with high failure rate during R&D process is a hindrance to innovation in developing countries most of which are challenged with financial instability and lack of incentive programs [20]. Majority of Kenyan pharmaceutical manufacturers have not entered into technology transfer agreements with multinational companies since procurement of these products is mainly donor funded and prequalification of manufacturing facilities by a stringent drug regulatory authority is mandatory [21].

Upgrading of manufacturing facilities and pharmaceutical market

Upgrading of manufacturing facilities to achieve compliance with GMP requires capital investment in appropriately designed premises that are fitted with quality impacting utilities, automated production lines, satisfactory quality management system and technical expertise. The establishment of the Kenya GMP roadmap by PPB implies that facilities that will be operational in Kenya by 2020 are those that will be compliant with the stringent international GMP standards. However, the products manufactured at the upgraded facilities may not be competitive for the local market. The implementation of the GMP roadmap may result in a scenario similar to that in India

which enforced GMP standard in 2005 that led to the closure of 70 small and medium companies by 2009 and the simultaneous emergence of GMP compliant and innovative companies which now dominate the export market including to highly regulated countries [22]. India has the second highest number of USFDA approved pharmaceutical manufacturers after the USA [23].

Compliance with GMP standard was reported as a barrier to sustainability and expansion of small pharmaceutical manufacturers in Nepal where the local pharmaceutical industry has not pursued much upgrading and has focused on domestic market [24]. Quality Chemicals Limited, Uganda, which obtained WHO prequalification in 2010, has remained in business mainly due to the intervention and commitment by the government of Uganda to procure the products that are manufactured at this facility [25, 26]. Similarly, implementation of GMP in China led to production capacity underutilization with many manufacturers having to undergo economic adversities with a heavy debt burden [27]. The sales profiles of manufacturers F and N show that facility upgrading has a negative impact on sales to domestic market. However, facility upgrading to international standard as illustrated in this study serves as an avenue to global market and donor funded pharmaceutical procurements.

CONCLUSION

Nine of the 16 pharmaceutical manufacturers assessed complied with GMP standard in regard to manufacturing premises, HVAC, water systems, and quality control but were inadequate in R&D and personnel with specialized skills. Upgrading of two facilities resulted in reduced domestic sales. International GMP accreditation was not only a conduit to international and donor funded procurements but it also led to improved overall company sales.

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