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ABSTRACT

Objective: **To establish the quality of pharmaceutical products manufactured by the respective industries in Kenya and determine the effect of manufacturing practices on the quality of these products.**

Design: **Cross-sectional study.**

Setting: **Industries examined are in Nairobi, Kenya. Laboratory analysis was carried out using available facilities at Kenya Medical Research Institute and University of Nairobi, Faculty of Pharmacy.**

Interventions: **Structured Questionnaires were administered to examine how the code of good manufacturing practices has been used in the production of each pharmaceutical product by respective companies. Questionnaires designed to evaluate the distribution and carry out limited post-market surveillance study were administered to community pharmacy outlets. Drugs were sampled and analyzed for their quality according to the respective monographs.**

Main Outcome Measures: **The questionnaires administered to the industry included the source of raw materials, quarantine procedure before and after manufacture, manufacturing procedure, quality audit, quality assurance procedure, equipment, and staff. That administered to the pharmacy outlet included availability, affordability and acceptability of locally manufactured pharmaceutical products. Quality analysis of products involved the establishment of the chemical content, dissolution profile, friability, uniformity of weight and identity. For antibiotic suspensions the stability after reconstitution was also determined.**

Results: **There were 15 respondents and two non-respondents from the industry and six out of nine respondents from the pharmacy outlets. The ratio of qualified staff to product range produced seemed to influence product quality. Industries producing several products with only limited number of pharmaceutical staff had more products failing to comply with pharmacopoeia specifications compared to those producing only few products. Nevertheless, all companies are well equipped with quality control equipment, in accordance with type of product manufactured. Private pharmacies stocked few of the locally manufactured products. The reason, they said, was due to low doctor and/or patient acceptance. Compliance with quality specifications as set out in respective monographs was overall 76%.**

Conclusion: **Although the local pharmaceutical industries have adopted good manufacturing practices leading to many good quality products currently in commerce, these manufacturing practices are not comprehensive and measures need to be taken to continue improving them.**

INTRODUCTION

Pharmaceutical manufacture is a significant aspect of Kenya's industrial sector. There are 40 registered pharmaceutical manufacturers in Kenya (Personal communication, Pharmacy and Poisons Board, 2003). Some of these are subsidiaries of multinational pharmaceutical companies. The companies generally repackage drugs or produce pharmaceutical dosage forms from imported raw materials. As it responds to challenges and opportunities, the generic pharmaceutical industry will continue to be a major force shaping the economics of medication(1). In view of the variability of drug manufacturing practices and the adventitious

effect of counterfeit(2), it has become necessary to regulate the manufacture of drugs and their distribution. In all countries, regulatory authorities apply a code of good manufacturing practices(3). In developing countries, the development of national drug policies(4,5) has been necessary to ensure the availability of quality pharmaceutical products. However, there are still many difficulties in effecting quality assurance measures on pharmaceutical products circulating in commerce. Poor quality of drugs has been linked to counterfeiting of medicines(6), chemical instability especially in tropical climate(7) and poor quality control during manufacturing(8).

Since 1982 the government of Kenya has been making efforts in maintaining quality assurance of pharmaceutical products through legislation and limited market surveillance. The registration of pharmaceutical products has been going on and efforts are being made to ensure that the local manufacturers comply with WHO's code of Good Manufacturing Practices(9). Although imported finished products supply almost 50% of the Kenyan market, the pharmaceutical manufacture is considered a significant aspect of Kenya's industrial sector. As concerns about reducing health care cost increases, the use of generic medicines continue to gain support globally(10,11). The importance of producing quality pharmaceutical products, both generic and innovator brand products cannot be overemphasised.

The drugs procured from both local and international suppliers are assumed to be of good quality, although this is not always the case. Several reports from developing countries have indicated the presence of poor quality drugs, both locally manufactured and imported(12-14). In Kenya, the extent of problems with quality of drugs has been documented in a series of articles on the work of the Drug Analysis and Research Unit (DARU) of the University of Nairobi(15-17). In order to ensure a sustained growth of the local industry, it is necessary to ensure that good manufacturing practices (GMP) are adhered to and quality products are released to the consumer. This can readily be achieved through regular surveillance studies. Such studies may provide information on the general extent of quality and, where possible identify the course for poor quality so that corrective measures may be put in place.

In this study, some locally manufactured pharmaceutical products that would present manufacturing challenges in any factory were identified and their quality determined. The industries that manufacture these products were assessed for their capacity to produce quality drugs. The main aim was to establish the quality of pharmaceutical products manufactured by the respective industries in Kenya and to determine the effect of manufacturing practices on the quality of these products.

MATERIALS AND METHODS

Linkages were established with pharmaceutical manufacturing industries in Kenya from whom scientific information regarding manufacturing practices was obtained using well designed questionnaires. Questionnaires were administered to 17 manufacturing plants. Questionnaires sought to capture data on the source of raw materials, quarantine procedure before and after manufacture, manufacturing procedures quality audit, quality assurance procedure, equipment, and staff. Another set of questionnaires that sought data on availability, affordability and acceptability of locally manufactured pharmaceutical products was administered to a total of nine community pharmacy outlets in Nairobi.

Drug samples of different categories of drug products selected from among the most commonly used pharmaceuticals were obtained from the industries during the first visit. Drug products similar to those obtained from the industry were also purchased from community pharmacy outlets in Nairobi when they were available.

Various quality-indicating parameters were evaluated to establish the quality of selected products. The methods and procedures used are those set out in respective monographs in the relevant pharmacopoeias. Products for which a more selective assay method was not available in the pharmacopoeia were analyzed using analytical liquid chromatography (LC) method(18).

Assay: Chemical content of ampicillin in ampicillin 250 mg capsules and ampicillin dry suspension (125mg/ml) and that of phenoxymethylpenicillin tablets was determined using iodometric titration according to respective USP 24 monographs (19). For ampicillin dry suspension, the chemical content seven days after reconstitution was also determined to evaluate the stability of the suspension.

The contents of chlorpropamide tablets; paracetamol syrup; diazepam injection; chloramphenicol capsules; and methyldopa tablets were determined using UV spectrophotometric assay according to procedures described in respective monographs in the BP(20). The chemical content of sulphamethoxazole/trimethoprim tablets was determined using LC as described in the USP(19).

Phenobarbitone, phenytoin and carbamazepine content in respective tablets were analyzed using a selective LC method (18) as follows. An isocratic liquid chromatographic system consisted of an L-6000 A pump (Merck-Hitachi, Darmstadt, Germany), an electronic integrator HP 3394 A (Hewlett - Packard, Avondale, PA, USA) and a Gilson 112 UV detector (Gilson, Villler le Bel, France) set at 254 nm. The mobile phase comprised acetonitrile, 0.2M potassium phosphate buffer pH 7.6, tertiary butanol and water in the ratio 25:10:5:60, v/v, at a flow rate of 1 ml/min. A column of 250 x 4.6 mm l.D. packed with A PLRP-S 100 R, 8µm (Polymer laboratories, Church Stretton, Shropshire, UK) was maintained in a water bath at 60°C. Standard solutions of phenobarbitone, phenytoin or carbamazepine were prepared by dissolving 30 mg of phenobarbitone, 50 mg of phenytoin or 25 mg of carbamazepine in 50ml mobile phase. Aliquots (1.00 ml) of each solution were diluted to 10.0ml. The test solution for phenobarbitone, phenytoin or carbamazepine tablets were prepared by weighing and powdering 20 tablets of each product, mixing and extracting 30.0 mg, 50.0 mg

or 25.0 mg respectively in 50.0 ml mobile phase. In each case, the resulting solution was filtered through a 0.2 µm membrane and 1.0 ml diluted to 10.0 ml in mobile phase. 20 µl of each solution was injected for chromatography.

Dissolution test: Dissolution profiles for chlorpropamide, phenoxymethylpenicillin potassium, carbamazepine and phenorbanitone tablets as well as for ampicillin capsules were obtained by performing a dissolution test using an Erweka DT6 dissolution tester (Erweker, Milford CT, Germany). The dissolution media, rotation speed and type of stirrer were as outlined in the BP(20). The active ingredients present in the dissolution medium at 45 min. were analyzed using prescribed analytical procedures in the respective monographs.

Friability test: Erweka tablet friabilator (Erweker, Milford CT, Germany) was used to determine the friability of carbamazepine, phenorbabitone and co-trimoxazole tablets according to the method described in the BP.

Uniformity of weight: The test for uniformity of weight was carried out as prescribed in the BP.

Particulate matter in large volume infusions: Three types of 500 ml infusions, dextrose 5%, normal saline and Hartmann's solution were visually examined for the presence of visible particulate matter by inverting the bottle and placing against light.

RESULTS

Quality Analysis: The results on friability, dissolution, weight uniformity, disintegration time, identity and assay of active ingredients for each sample examined are summarized in Table 1. Out of 63 samples analyzed for chemical content, 57 (90%) complied with respective pharmacopoeia limits. The six (10%) samples that did not meet pharmacopoeia specification for chemical content were three samples of paracetamol suspension, two of phenytoin tablet samples and one of sulfamethoxazole/ trimethoprim suspension. Two samples of paracetamol suspension contained quantities of active ingredient higher than the pharmacopoeia specifications while the third sample contained quantity lower than the specified limits. Phenytoin samples from the same manufacturer had the batch sampled from the manufacturing plant containing active ingredient twice the pharmacopoeia limits while a different batch sampled from pharmacy outlet contained active ingredient slightly below the pharmacopoeia limits. The trimethoprim content of sulfamethoxazole/trimethoprim suspension was slightly above label claim.

Table 1

Quality evaluation of samples

Product	Source	Friability (% wt. loss)	Dissoln Q (%)	UOW	Stability (% tolerance)	ID	Content
Ampicillin	C		97.4	-		+	98.17
250 mg	D		101.3	+		+	107.6
Caps	F		92.3	-		+	106.3
	L		90.0	-		+	97.45
	M		94.2	+		+	102.02
	M*		ND	+		+	108.42
	N		95.1	+		+	103.29
Chloramphenicol 250mg	N		-				98.4
Pen V250	D		96.4	+			114.93
mg tablets	N*		89.1	-			112.6
Chlorpropamide	F		35.3	+			98.8
250mg tabs	J		100.7	+			100.1
	J*		34.3	+			99.6
	J		N/D	+			100.9
Methyldopa	J						102.9
250mg tabs	J*						103.2
Carbamazepine	J*	0.48	93.7	+			96.8
250mg tabs	P	0.07	67.1	ND			96.1
Phenytoin	N			+			191.9
50 mg tabs	N*			ND		93.1	
Phenobarbitone	F	1.85	95.7	-			95.9
30 mg Tabs	J	0.11	90.5	+			92.9
	J*	N/D	94.8	ND			98.4
	N	0.04	93.3	+			98.8
Sulfameth	B	0.58		+			95.0/95.5
oxazole/	C	0.49		+			94.1/93.4
Trimethoprim	D	0.26					98.1/94.6
Tabs	F	N/D		+			103.1/99.2
	L	0.59		+			97.7/90.8

	M	0.18	+				99.2196
	P	0.12	+				98.4/100
Ampicillin	C			88.14	+		93.5
Suspension	D			81.29	+		104.8
	E			97.23	+		101.4
	J*			98.27	+		106.4
	M			ND	+		107.2
Sulfameth-	A						101.8/94.4
oxazole/	B						100.7/98.0
Trimethoprim	C						101.4/94.2
suspension	D						108.2/92.6
	E						105.9/100.6
	H						109.7/111.0
	K						100.4/99.2
	L						104.2/99.0
	M						104.9/99.8
	N						104.4/107.1
Paracetamol	A						2.37#
Suspension	B						2.41#
	C						3.03#
	D						2.48#
	G						2.13#
	H						2.45#
	J						2.52#
	K						2.44#
	L						2.48#
	M						2.78#
Chloramphenicol	A						96.3
	A*						96.8
ear drops	D						96.1
	E						162.8
	F						100.3
	L						91.9
Diazepam Injection	N				+		107.7

*= products sampled from pharmacy outlets. +, complies; -, does not comply, #= given as % w/v of stated amount, Dissoln= dissolution tolerance; UOW= uniformity of weight; ID= identity test; ND= not determined., Content limits: ampicillin and Pen V, 90-120% (USP); ampicillin % tolerance, not less that 80% label claim (after 7 days); diazepam, 90-110% (BP); chloramphenicol, carbamazepine, phenytoin and methyldopa, 95-105% (BP); chlorpropamide and phenobarbitone, 92.5-107.5% (BP). sulphamethoxazole/ trimethoprim, 90-110% (USP); paracetamol suspension, 2.28-2.52% w/v (BP); chloramphenicol ear drops, 90-110% (BP). Friability limit: % wt loss not greater than I (BP). Dissolution tolerance limits: not less than 75% in 45 min (BP & USP).

Table 2

Number of staff, products manufactured and quality control (QC) equipment

Industry	A	B	C	D	E	F	G	H	I	J	K	L	M	N	P
Staff#	>50	>50	11-20	>50	31-40	>50	41-50	>50	>50	>50	11-20	41-50	>50	> 50	41-50
Pharmacists	2	16	3	6	1	5	6	1	1	5	2	3	3	6	2
Products manufactured	98	30	41	100	36	>100	20	20	5	121	20	45	95	290	55
Product types	9	5	5	9	9	13	5	8	1	14	8	12	16	15	5
QC equipment	4	7	3	4	3	5	4	3	2	6	4	4	6	7	3
Raw materials rejected	0	4	6	4	4	4	64	6	0	5	0	2	1	4	2
Materials recalled	0	0	3	0	2	0	0	1	0	6	0	1	1	1	0
Failure rate*	0/4	0/3	2/5	1/7	0/3	3/5	1/1	1/2	0/3	1/10	0/2	1/5	1/6	4/8	1/2

#= Staff involved in mufacturing
*= Given as number of products failing to comply with specifications/total number evaluated

Of the 17 samples subjected to dissolution test 14(82%) complied with the BP limits for dissolution tolerance while three (18%) failed to comply. The three that failed were two samples of chlorpropamide and one sample of carbamazepine. Eleven samples were subjected to friability test and one sample of phenobarbitone tablet failed to comply with the BP specification for friability limits.

The test for uniformity of weight resulted in 50% (4 out of 8) compliance for the capsule products and 83 % (15 out of 18) compliance for the tablet formulations. Large volume infusions examined were all found to be free of particulate matter.

Manufacturing practices evaluation: A total of 17 (three multinational subsidiaries and 14 locally owned) industries were assessed using questionnaires designed to capture how respective companies have used the code of good manufacturing practices in the production of each pharmaceutical product. The questionnaires were self-administered, because the required details were not readily available at the time of the visit. There were 15 respondents and two non-respondents. Table 2 gives the results of the GMP compliance assessment. Three of the 15 respondents produce a wide range of products. Industry N produces the largest range of pharmaceutical products (290) and has engaged six pharmacists. Half (4 out of 8) of the products analyzed from this company did not comply with the respective pharmacopoeia specifications for quality. Similarly, Industry F with a range of more than 100 products and has five pharmacists, had three products out of five analyzed fail to comply with quality specifications. Industry B, a subsidiary of a multinational company produce 30 products and has 16 pharmacists of which seven are directly involved in production and quality assurance activities. All the products from industry B that were analyzed complied with the pharmacopoeia specifications for quality. The number of different quality control equipment available in the industries evaluated ranged from 2 to 7. Twelve out of 15 industries (80%) had rejected one or more raw materials from suppliers within five years from the study period.

Questionnaires constructed to evaluate the distribution and patient acceptability of locally manufactured products were administered to a total of nine community pharmacy outlets. There were six respondents and three non-respondents. Availability in the pharmacy outlets of the eight locally manufactured drug products chosen for the study was found to be as follows: Co-trimaxazole tablets/suspension was available in all the six pharmacies; chlorpropamide tablets in three pharmacies; ampicillin capsules/suspension and levamisole tablets/suspension in two pharmacies; dextrose injection and diazepam injection in one pharmacy; while methyldopa tablets and digoxin injection were not stocked in any of the pharmacy outlets visited. Products frequently subjected to complaints included diazepam injection, ampicillin capsules metronidazole and ibuprofen, among others.

DISCUSSION

Drug products were assayed to verify label claims and to ensure that they conform to specifications in the official monographs. Overall 76% compliance to quality specifications shows that there is still room for improvement. Content non-compliance (10%) may be attributed to inadequate production process validation and quality control during manufacturing process. Dissolution rate is an important physical characteristic of tablet, capsule or other oral solid dosage forms. Compliance of drug products to dissolution tolerance specification is an indicator to their bioavailability. The dissolution tolerance below the pharmacopoeia limits of not less than 75% in 45 minutes that was obtained for some chlorpropamide tablets (34.7%) and some carbamazepine tablets (61.7%) may be due to formulation problems.

There were marked problems with uniformity of weight. Weight uniformity also depends on the manufacturing process. Most local companies still carry out capsule filling by semi-manual process. In view of this, capsule dyes and tablet hoppers must be adjusted as frequently as required in order to obtain reproducible product quality. Large volume infusions were only examined for the presence of particulate matter. They were all found to be free of foreign matter indicating that they were prepared under prescribed conditions that preclude introduction of extraneous material.

Inadequacy of appropriate qualified personnel may be a contributing factor to poor compliance to GMP in the industry. Pharmacist in the industry is responsible for all the activities that influence the production of quality medicines. He/she is involved in conducting research into the formulation, production, storage, quality control and distribution of medicines. He/she develops legally recognised standards, and advice on the government controls and regulations concerning the manufacture and supply. of medicines. A pharmacist may also be involved in management of the pharmaceutical company. Appropriate number of pharmacists are necessary if all these functions are to be adequately managed with the aim of producing quality products. In this study it was observed that industries that engaged in the manufacture of more than 100 drug products and had few pharmacists showed higher failure rates compared to those producing a smaller range of products but engaged more pharmacists. Nevertheless, it was noted that all companies have well equipped quality control laboratories with respect to the types of product manufactured. For example, all companies producing methyldopa were found to have a polarimeter for determination of optical rotation. From the survey results it is apparent that most industries reject substandard raw materials. This reflects the importance these industries attach to the contribution of quality raw materials.

The limited post-market surveillance study revealed that some locally manufactured products were not stocked in the pharmacy outlets mainly because they were slow moving as a result of low doctor and/or patient acceptance. Products frequently subjected to complaints included diazepam injection, ampicillin capsules, metronidazole and ibuprofen, among others. The formulation of diazepam injection is complex and bioavailability problems exist. Products like ampicillin are subject to abuse thus increasing drug resistance. Metronidazole may also have efficacy problems probably due to abuse. Ibuprofen, a sugar coated tablet may present with poor physical characteristics due to poor coating. There may therefore be varying factors contributing to poor availability and acceptability of some locally manufactured products in Kenya.

In conclusion, the results of this study lend support to the contention that the main reason for poor quality may be inadequate GMP. It can be concluded that local industries endeavor to adhere to cGMPs, despite the economic constraint and shortage of trained personnel. However, these manufacturing practices are not comprehensive. The enforcement of regulatory measures is needed to generally achieve internationally accepted standards of good manufacturing practices

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