Quality Performance of Drugs Analyzed in the Drug Analysis and Research Unit (DARU) during the Period 2006-2010

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During the period 2006-2010, the Drug Analysis and Research Unit analyzed 583 samples. The samples comprised 50.6% local and 49.4% imported products. Samples were subjected to compendial or in-house specifications. The failure rate was 12.2% for local products and 14.2% for imports. Antibacterial products recorded the highest failure rate (21.6%) while anticancers and drugs acting on the gastrointestinal, respiratory and reproductive systems all passed in the tests performed. The failure rate for antiprotozoals, antimalarials, antifungals, anthelminthics and analgesics was 14.3%, 12.5%, 11.8%, 8.9% and 11.5%, respectively.

Key words: DARU, drug product, assay, dissolution, antimicrobial, antimalarial

INTRODUCTION

The quality of a drug product is determined by product design, manufacturing process as well as storage and distribution practices [1]. Effective quality control testing entails use of compendial or validated in-house methods [2]. The Frost and Sullivan report of 2008 revealed that 72% of the drug products in the Kenyan market were imported and majority (58.7%) of the drugs in circulation were generics [3]. The limited investment in the local pharmaceutical manufacturing industry is mainly attributable to the high cost of production which undermines competitiveness in the market [4].

Market authorization for pharmaceuticals in Kenya is granted by the national drug regulatory authority, the Pharmacy and Poisons Board after requisite evaluation of drug registration applications. The applicants are required to submit a certificate of analysis from a recognized independent laboratory operating within Kenya or the East African Community. The three Kenyan laboratories accredited to carry out pre-registration analysis for this purpose are the National Quality Control Laboratory (NQCL), Drug Analysis and Research Unit (DARU) and Mission for Essential Drugs and Supplies (MEDS) laboratory [5].

Drug quality control in DARU has been conducted since 1980 [6]. The laboratory has published periodic reports on the quality performance of drug samples analyzed therein. Previous reports have shown a continued improvement in the quality of products analyzed in DARU. In the 1980s the overall failure rate ranged from 21.6% to 31.4%, dropping to 17.6-21.1% in the 1990s and 6.1% in the years 2001-2005 [6-16]. The number of samples submitted to the DARU laboratory has gradually increased over the years due to enhanced consumption by the growing Kenyan population and drive for enhanced exports [17,18]. This paper reports on the quality performance of samples analyzed in DARU during the period 2006-2010.

MATERIALS AND METHODS

Samples

The samples analyzed during the study period were received from manufacturers, importers, wholesalers, non-governmental organizations,

hospitals, analytical laboratories, research projects and to a lesser extent individual clients. Majority of the clients required analysis for product registration purposes. The laboratory was not involved in sampling of the products submitted for analysis.

The clients submitting samples to DARU are required to fill out a Request for Analysis (RFA) form with the following details: name and address of applicant (person or institution), name and telephone number of the contact person, name and type of product, manufacturer, batch number, manufacture and expiry dates, active ingredients, number of units submitted and the specific tests required. The RFA forms bear the name and signature of the person requesting for the analysis and similar details for whoever authorizes the request. The name of the person receiving the samples is filled in RFA and the forms dated. A laboratory number is assigned at the time of receiving the samples. Each pack or unit is labelled with the laboratory number for ease of sample tracking. These procedures are revised from those reported previously [6].

Methods

Compendial methods were used for products whose monographs were published in current editions of the British Pharmacopoeia [19], United States Pharmacopoeia [20] and International Pharmacopoeia [21]. In the absence of official methods, in-house specifications provided by the manufacturers or developed by DARU were applied. All methods were subjected to system suitability tests before application in analysis [2].

Tablets and capsules were subjected to tests for uniformity of weight, assay, and dissolution depending on the client's requests. Liquids and semi-solid dosage forms were analyzed for content, microbial load and pH. Ophthalmic and parenteral products were tested for sterility and assay. Bee honey samples were tested for antibiotic residues while water samples were tested for sterility or microbial contamination as requested. Identification and sterility tests were carried out on cetyl alcohol and needles, respectively.

RESULTS AND DISCUSSION

A total of 583 samples comprising 50.6% local and 49.4% imported were analyzed during the study period (Table 1). Whereas, the overall failure rate was 13.2%, it was 12.2% for local products and 14.2% for imported products. This observation is not consistent with previous DARU reports whereby local products have always recorded a higher failure rate. This indicates an improvement of the Good Manufacturing Practices (GMP) performance by the local manufacturing industry supported by improved regulatory supervision by the Pharmacy and Poisons Board [5].

Ninety eight samples (16.8%) comprising of amoxycillin, flucloxacillin, clotrimazole, aspirin and paracetamol were under stability study at the International Committee Harmonization (ICH) accelerated and real time conditions for zone four [22]. In this case, the batches under study were subjected to multiple analyses which were treated independently for purposes of data analysis.

None of the samples acting on the gastrointestinal, cardiovascular, respiratory and reproductive systems as well as the anticancer agents and skin preparations failed in the tests performed. Contrary to observations during the 2001-2005 period, eye preparations and nutrition products recorded a failure rate of 15.3% and 5.0%, respectively.

Table 1: Results of samples analyzed in DARU during the period 2006-2010

Drug class and name	Number of samples	Samples passed		Samples failed	
		Local	Imported	Local	Imported
1. Gastrointestinal system					
a. Antiulcer drugs					
Esomeprazole tablets	1	-	1	-	-
Esomeprazole injection	1	-	1	-	-
Lansoprazole/clarithromycin/tinidazole tablets	1	-	1	-	-
Pantoprazole tablets	1	-	1	-	-
Ranitidine tablets	2	1	1	-	-
Ranitidine injection	1	-	1	-	-
Rabeprazole/domperidone capsules	1	-	1	-	-
b. Antidiarrhoeal drugs					
Loperamide capsules	2	-	2	-	-
2. Cardiovascular system					
a. Hemostatics					
Etamsylate injection	1	-	1	-	-
b. Antihypertensives					
Carvedilol tablets	3	-	3	-	-
Enalapril tablets	1	-	1	-	-
Ramipril capsules	2	-	2	-	-
Telmisartan tablets	2	-	2	-	-
Telmisartan/HCTZ tablets	1	-	1	-	-
c. Hypoglycemic agents					
Metformin tablets	2	-	2	-	-
d. Hypolipidemics					
Rosuvastatin tablets	3	-	3	-	-
3. Eye preparations					
Atropine sulphate injection	1	-	1	-	-
Gentamicin eye/ear drops	4	3	-	-	1
Gentamicin/dexamethasone eye/ear drops	1	-	1	-	-
Ketorolac eye drops	1	-	1	-	-
Neomycin/betamethasone eye/ear drops	2	2	-	-	-
Neomycin/dexamethasone eye/ear drops	2	-	1	-	1
Ofloxacin eye drops	1	-	1	-	-
Timolol eye drops	1		1		
4. Antimicrobials					
a. Antibacterials					
Amoxycillin capsules	22	8	3	11	-
Amoxycillin suspension[b]	6	5	-	1	-

Table 1 ***continued***

Drug class and name	Number of samples	Samples passed		Samples failed	
		Local	Imported	Local	Imported
Amoxycillin/flucloxacillin capsules	-	1	-	-	-
Ampicillin capsules	1	-	-	1	-
Ampicillin suspension[b]	1	1	-	-	-
Ampicillin/cloxacillin injection	1	1	-	-	-
Ampicillin/cloxacillin capsules	1	-	1	-	-
Azithromycin tablets	7	-	5	-	2
Azithromycin suspension	2	-	-	-	2
Azithromycin/fluconazole/secnidazole tablets	2	-	1	-	1
Benzyl penicillin injection	1	-	1	-	-
Cefaclor suspension[b]	1	-	1	-	-
Cefaclor capsules	2	-	2	-	-
Cefadroxil suspension[b]	2	-	2	-	-
Cefixime capsules	4	-	3	-	1
Cefixime tablets	2	-	2	-	-
Cefixime suspension[b]	1	-	1	-	-
Cefotaxime injection[b]	2	-	2	-	-
Ceftriaxone injection[b]	3	-	3	-	-
Ceftriaxone/sulbactam injection[b]	1	-	1	-	-
Cefpodoxime tablets	2	-	1	-	1
Cefpodoxime suspension	1	-	1	-	-
Ceftazidime injection[b]	2	-	2	-	-
Cefuroxime axetil tablets	9	-	7	-	2
Cefuroxime sodium injection	3	-	3	-	-
Cephalexin capsules	1	1	-	-	-
Ciprofloxacin tablets	3	1	2	-	-
Chloramphenicol capsules	1	-	1	-	-
Chloramphenicol powder[a]	1	-	1	-	-
Chloramphenicol sodium succinate injection	1	-	1	-	-
Clarithromycin tablets	2	-	2	-	-
Clarithromycin suspension[b]	1	-	1	-	-
Co-amoxiclav tablets	1	-	-	-	1
Co-amoxiclav suspension[b]	3	-	3	-	-
Cotrimoxazole tablets	2	-	1	-	1
Cotrimoxazole suspension	1	-	1	-	-
Erythromycin ethyl succinate suspension[b]	27	2	19	-	6
Erythromycin stearate suspension[b]	1	-	-	1	-
Erythromycin ethyl succinate powder[a]	26	1	17	-	8
Erythromycin stearate tablets	20	3	14	-	3
Flucloxacillin capsules	4	4	-	-	-
Flucloxacillin injection	1	1	-	-	-
Gentamicin injection	8	8	-	-	-
Kanamycin injection	1	-	1	-	-
Levofloxacin tablets	1	-	1	-	-

Table 1 *continued*

Drug class and name	Number of samples	Samples passed		Samples failed	
		Local	Imported	Local	Imported
Levofloxacin infusion	1	-	1	-	-
Vancomycin injection	1	-	1	-	-
Meropenem injection	5	-	5	-	-
Norfloxacin tablets	2	-	1	1	-
Norfloxacin/tinidazole tablets	1	-	1	-	-
Ofloxacin/ornidazole tablets	2	-	2	-	-
Ofloxacin tablets	2	-	1	-	1
Oxytetracycline injection[v]	1	-	1	-	-
Procaine penicillin injection[b]	1	1		-	-
Streptomycin sulphate injection[b]	1	-	1	-	-
Tetracycline capsules	1	-	1	-	-
b. Anthelmintics					
Albendazole tablets	1	-	1	-	-
Albendazole suspension[v]	29	25		4	-
Ivermectin powder[a]	1	-	1	-	-
Levamisole/oxyclozanide suspension[v]	9	9	-	-	-
Levamisole solution[v]	1	1	-	-	-
Mebendazole tablets	1	-	1	-	-
Mebendazole suspension	1	1		-	-
Praziquantel tablets	1	-	1	-	-
Triclabendazole suspension[v]	1	1	-	-	-
c. Antiprotozoals					
Metronidazole tablets	2	-	2	-	-
Nitazoxanide tablets	2	-	1	-	1
Secnidazole tablets	1	1	-	-	-
Tinidazole tablets	2	-	2	-	-
d. Antimalarials					
Amodiaquine suspension	1	-	-	1	-
Amodiaquine tablets	1	-	-	-	1
Arteether injection	1	-	1	-	-
Artemether injection	3	-	3	-	-
Artemether/lumefantrine tablets	4	1	3	-	-
Artemether/lumefantrine suspension	3	1	1	-	1
Artesunate injection[b]	2	-	2	-	-
Artesunate/amodiaquine tablets	3	1	2	-	-
Chloroquine phosphate tablets	4	4	-	-	-
Chloroquine phosphate injection	1	-	1	-	-
Dihydroartemisinin/piperaquine tablets	2	-	1	-	1
Lumefantrine powder[a]	1	-	1	-	-
Quinine sulphate tablets	3	3	-	-	-
Quinine dihydrochloride syrup	1	1	-	-	-
Quinine dihydrochloride injection	1	-	1	-	-
Sulphadoxine/pyrimethamine tablets	1	-	1	-	-

Table 1 *continued*

Drug class and name	Number of samples	Samples passed		Samples failed	
		Local	Imported	Local	Imported
e. Antivirals					
Aciclovir injection	1	-	1	-	-
Lamivudine tablets	1	-	1	-	-
Stavudine/lamivudine/nevirapine tablets	1	-	1	-	-
f. Antifungals					
Amphotericin B injection[b]	6	-	4	-	2
Clotrimazole powder	12	12	-	-	-
Fluconazole tablets	1	-	-	-	1
Ketoconazole tablets	2	1	1	-	-
Nystatin tablets	5		5	-	-
Nystatin vaginal tablets	5	1	4	-	-
Nystatin suspension	3	2	-	-	1
g. Pesticides					
Benzyl benzoate liquid[a]	1	-	1	-	-
Dichlorophen based milking salve[v]	24	19	-	5	-
h. Antiseptics					
Povidone iodine[a]	1	-	-	1	-
Isopropyl alcohol solution	1	1	-	-	-
i. Insecticides					
Abamectin injection[v]	1	-	1	-	-
Alpha cypermethrin solution	3	3	-	-	-
5. Nervous system					
a. Analgesics					
Aspirin lysine injection	1	-	1	-	-
Aspirin tablets	8	6	-	2	-
Diclofenac sodium tablets	3	-	3	-	-
Diclofenac sodium injection	1	-	1	-	-
Ibuprofen tablets	2	-	1	-	1
Ibuprofen suspension	1	1	-	-	-
Indomethacin capsules	1	-	1	-	-
Paracetamol tablets	23	19	3	-	1
Paracetamol syrup	18	15	-	3	-
Paracetamol suppositories	1	-	-	-	-
Paracetamol/ascorbic acid powder	1	-	1	-	-
Paracetamol/ibuprofen/caffeine tablets	1	-	1	-	-
b. Antinflammatory agents					
Hydrocortosone sodium succinate injection	3	-	3	-	-
c. Anti-epileptics					
Sodium valproate tablets	2	-	2	-	-

Table 1 ***continued***

Drug class and name	Number of samples	Samples passed		Samples failed	
		Local	Imported	Local	Imported
d. Anaesthetics					
Lidocaine injection	1	-	1	-	-
Bupivacaine injection	1	-	1	-	-
Ketamine injection	1	-	1	-	-
6. Respiratory system					
Terbutaline/bromhexine/guaifenesin/ menthol syrup	1	-	1	-	-
Salbutamol/bromhexine/guaifenesin/ menthol syrup	1	1	-	-	-
Salbutamol syrup	1	1	-	-	-
Carbocisteine[a]	1	1	-	-	-
Ephedrine HCl[a]	1	1	-	-	-
7. Reproductive system					
Ergometrine injection	1	-	1	-	-
Levonorgestrel implant	1	-	1	-	-
Medroxyprogesterone injection	2		2		
8. Anticancer agents					
Carboplatin injection	2	-	2	-	-
Fluorouracil injection	1	-	1	-	-
Paclitaxel injection	2	-	2	-	-
9. Skin preparations					
Tretinoin[a]	1	-	1	-	-
Ketoconazole cream	1	-	1	-	-
Nystatin ointment	2	2	-	-	-
10. Nutritional products					
a. Vitamins					
Menadione powder	1	-	1	-	-
b. Bee honey					
Bee honey	78	77	-	1	-
c. Electrolytes					
Glucose IV infusion	3	-	3	-	-
Sodium chloride injection	5	2	3	-	-
Sodium bicarbonate injection	2	-	2	-	-
Sodium lactate injection	1	-	1	-	-

Table 1 ***continued***

Drug class and name	Number of samples	Samples passed		Samples failed	
		Local	Imported	Local	Imported
d. Waters					
Water for injection	5	-	5	-	-
Mineral water	1	1	-	-	-
Stream water	4	-	-	4	-
11. Miscellaneous products					
a. Medical devices					
Needles	1	-	1	-	-
b. Emulsifiers					
Cetyl alcohol	2	-	2	-	-
Totals number of samples	**583**	**259**	**247**	**36**	**41**

DARU – Drug Analysis and Research Unit, a – drug substance powder, b – drug product powder, v – veterinary product

With the exception of pesticides, for which the sample size was very small, antibacterial drugs registered the highest failure rate of 21.6%. This represents an increase in the failure compared to results obtained in DARU since the 1991-1995 period (Table 2). Eleven amoxycillin capsules samples failed in the test for weight uniformity (6) and assay (5). All the non-compliant samples were of local origin. Eight out of the 26 (30.8%) erythromycin ethyl succinate bulk samples analyzed failed in the test for related substances while 22.2% of erythromycin ethyl succinate suspensions failed in the assay test. Three out of 20 (15%) erythromycin stearate tablets samples failed in the assay. There was a relatively high proportion of non-compliant azithromycin suspensions (100%) and tablets (28.6%). Other antibacterials with quality problems were cefixime, cefpodoxime, cefuroxime axetil, co-amoxiclav, cotrimoxazole and ofloxacin

Quality of antibiotics have been of concern for the last three decades. Except in the 2001-2005 period, the failure of antibiotics has been high (10.7-31.5%). This trend could be contributory to the emergence of resistance against the commonly used antibiotics such as ampicillin, tetracycline and co-trimoxazole during these periods [23].

About 12.5 % of the antimalarial drugs failed in the assay or microbial load tests. This was the lowest failure rate since the 1991- 1995 period (Table 2). One of the non-compliant samples was a counterfeit product of dihydroartemisinin/piperaquine which was submitted to the laboratory by the vendor of the genuine product. The counterfeit product was found to lack piperaquine while its dihydroartemisinin content was 66.7% of the label claim. The low proportion of sulphadoxine/pyrimethamine (S/P) samples analyzed during the study period is due to the policy shift of first line treatment for malaria in Kenya from S/P to artemether/lumefantrine (AL) in 2006 [24].

Table 2: Failure rates (%) of antimicrobials analyzed at DARU during the period 1980-2010

Therapeutic categories	Jan 1980 - Jun 1981	Jul 1981 - Dec 1982	1983 - 1986	1987 - 1990	1991 - 1995	1996 - 2000	2001 - 2005	2006 - 2010
Antibacterials	14.9	31.5	30.0	26.2	18.4	10.7	3.2	21.6
Anthelmintics	a	a	14.3	0	25.0	37.5	10.0	9.1
Antimalarials	-	14.3	6.7	0	23	27.7	26.9	12.5
Antiprotozoals	0	a	20	0	0	14.3	0	14.2
Antifungals	a	a	a	a	100	33.3	0	11.8
Antiretrovirals	a	a	a	a	a	28	3.4	0
Antituberculars	20.0	20.2	a	a	40.0	0	0	a

a: No drugs were analyzed during the period

Among the antifungals, one third of amphotericin B and nystatin suspension samples failed in the weight uniformity test and assay test, respectively (Table 1) while the only sample of fluconazole tablets analyzed failed in the dissolution test. The overall failure rate for this class of drugs was 11.8% representing an increase in the failure rate compared to 2001-2005 period.

Albendazole suspension for veterinary use accounted for all the failures (8.9%) in the anthelmintics category while among the antiprotozoals, nitazoxanide tablets were non-compliant with specifications.

Only 2 samples of antiretroviral drugs were analyzed during the study period unlike in the 2001-2005 period when 29 samples were encountered. This can be attributed to the antiretroviral therapy programme sponsored by the Kenyan government whereby only pre-qualified firms supply the drugs which limits their availability in general distribution. For the same reason no antituberculars were encountered during the study period [25,26]. However, to ensure consistent supply of quality of these classes of drugs, post distribution surveillance is still necessary [16,27].

Analgesics recorded a failure rate of 11.5% attributable to dissolution problems with aspirin and ibuprofen tablets as well as assay of paracetamol tablets and syrups. This class of drugs has had a low failure rate (<10%) since the 1991-1995 period according to DARU quality control reports [10,14,15].

Milking salve samples were subjected to the assay of dichlorophen whereby the failure rate was 20.8%. The stream water samples analyzed were submitted by an individual client to resolve a dispute concerning discharge of waste water into a communal stream. The samples analyzed were taken at different points upstream and downstream as well as the effluent and all were found to be contaminated with *Entero-bacteriaceae, Escherichia coli*, aerobic bacteria and fungi. The WHO guidelines specify the control of coliforms and other pathogenic microorganisms in drinking water [28].

In the nutrition category, honey samples were tested for antibiotic residues with a 98.7% pass rate. Oxytetracycline was detected in only one honey sample. This is the first time honey samples were received in the laboratory for analysis since its inception. There is increased demand for bee products such as honey, royal jelly and propolis leading to investment in commercial bee farming both for local and export market. In common practice, antibacterial agents are used to prevent infections in apiaries [29]. Published reports indicate presence of traces of these drugs in honey samples [30-31]. Quality control of bee products is therefore essential.

CONCLUSION

During the period 2006-2010 the overall failure rate of the drugs analyzed in DARU was higher (13.2%) than in the 2001-2005 period when it was 6.1%. Antibacterial drugs had the highest failure rate (21.7%) followed by eye preparations in contradistinction to previous reports in which antimalarials performed poorly. None of the samples acting on the gastrointestinal, cardiovascular, respiratory and reproductive systems as well as the anticancer agents and skin preparations failed in the tests performed. The results obtained underscore the need for more stringent scouting by the Pharmacy and Poisons Board to ensure consistent circulation of good quality medicines in the Kenyan market. This can be achieved through sustained regular post-market surveillance and efficient pharmacovigilance reporting systems accompanied by appropriate regulatory actions based on findings.

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