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Quality Control Report of Drugs Analyzed in the Drug Analysis and Research Unit during the Period 2011-2015

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During the period 2011-2015, the Drug Analysis and Research Unit (DARU) analyzed 1972 drug samples. The samples consisted of 21.5% locally manufactured and 78.2% imported products while the origin of 0.3% of products was indeterminate. Samples were subjected to compendial and/or in-house analytical specifications. The overall non-compliance rate was 4.5% comprising 2.5% local products and 2.0% imports. High failure rates were recorded for uterotonics (37.5%), hemostatics (33%), anthelmintics (17%) and anticancers (10.5%) while ophthalmic, immunomodulatory, musculoskeletal and endocrine drugs all complied with the quality acceptance criteria. Erectile dysfunction drugs, received by the laboratory for the first time, all complied with specifications. The results obtained demonstrate an improvement in the quality of samples submitted to DARU when compared to previous performance.

Key words: DARU, drug analysis, drug class, pharmacovigilance, post-market surveillance

INTRODUCTION

Human and veterinary medicines must conform to specifications for quality, safety and efficacy (QSE) in order to elicit the desired pharmacological responses. With regard to human pharmaceuticals, quality criteria are defined in the International Conference on Harmonization (ICH) technical requirements for registration [1]. Quality control (QC) of pharmaceuticals embodies specialized analysis for conformance with acceptance criteria as defined in the official compendia (pharmacopeias) or in-house specifications. This is integral to systematic drug evaluation to meet the requisite QSE attributes for the purpose of market authorization (MA). Additionally, QC plays a critical role in supporting pharmaceutical manufacturing, batch release, post-market surveillance (PMS) and pharmacovigilance (PV) frameworks.

Quality assurance of medicines in specific jurisdictions is a function of the National Drug Regulatory Authorities/Agencies (DRA). In Kenya, the Pharmacy and Poisons Board (PPB) and Veterinary Medicines Directorate are mandated to control human and veterinary products, respectively [2, 3]. A critical function of the DRA is the market authorization of drugs consequent to comprehensive dossier evaluations as defined by the ICH guidelines. In fulfilment of the Common Technical Document (CTD) requirements for drug registration, QC reports from accredited laboratories are compiled with each submission [4]. Locally, three laboratories are accredited for this purpose, namely, National Quality Control Laboratory (NQCL), Drug Analysis and Research Unit (DARU) and Mission for Essential Drugs and Supplies (MEDS) laboratory [5].

Whereas pre-registration QC of drugs is essential for regulatory approval, it cannot guarantee the quality of products in circulation after MA is granted. Subsequent commercial batches of the registered product may not be equivalent to the initial one submitted for registration. Several studies have demonstrated occurrence of substandard products in the market especially in developing countries [6, 7]. In this regard, the competent authorities bear the responsibility of putting in place PMS and PV schemes to ensure that consistent quality medicines are accessible to

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end users. The Pharmacovigilance department of the PPB utilizes 'pink forms' for reporting poor quality medicines [8].

Drugs marketed in Kenya are either locally manufactured or imported. About 70% of pharmaceuticals circulating within the Kenyan market are imported mainly from India and China [9]. The market dominance by imports has been a concern for the last four decades especially in the context of the government's Big Four Agenda which aspires to the attainment of a robust local manufacturing industry [10].

Since its inception in 1977, the DARU laboratory has been publishing periodic reports on the quality performance of samples analyzed therein [11-17]. The previous QC reports have demonstrated continued improvement of the quality of samples tested over the last four decades. Improvement in the quality of anti-infective agents during this period is encouraging in the context of concerted efforts to limit antimicrobial resistance. Furthermore, these findings play an important role in monitoring quality performance of drugs in the market and could elicit policy interventions intended at diminishing the market burden of substandard and falsified medicines [17]. This paper reports the quality control results of samples analyzed in the DARU laboratory during the 2011-2015 period.

MATERIALS AND METHODS

Samples

The samples submitted to DARU for analysis during the study period were from local manufacturers, importers, wholesalers, non-governmental organizations, regulatory bodies and hospitals. The samples consisted of human medicines, veterinary products, vaccines, herbals, excipients and alcoholic beverages. Majority of the clients were manufacturers and importers who requested analyses in support of market authorization applications. Other reasons for analysis included PMS and PV investigations. The procedures for sample submission to DARU laboratory have been described previously [17].

Drugs for human use

Human drugs belonging to diverse therapeutic classes accounted for 87.6 % of the samples submitted with the top five being anti-infectives (786), neurological drugs (280), cardiovascular agents (176), respiratory drugs (151) and nutritional products (78).

Pharmacovigilance samples

Twenty-nine PV samples (1.5%) belonging to various pharmacological classes were received. They arose from PV investigations at points of use, particularly hospitals. These samples were accompanied by PV pink forms for poor quality medicinal products, specifying the sampling site, product details, nature of complaint and the complainant. The requisite tests to address specific complaint(s) were discerned at the point of sample submission through consultation between the laboratory and client. For instance, cyclophosphamide injections were subjected to stability testing under accelerated conditions for ICH stability zone IV to demonstrate that degradation was the cause of quality concerns [18].

Post market surveillance samples

There were 268 samples (13.6%) arising from PMS submitted by regulatory authorities, institutions and individual researchers. These included antimalarials (39), antibacterials (113), veterinary anthelminthics (112) and alcoholic spirit drinks (4), collected from the market for quality testing.

Veterinary drugs

A total of 244 (12.4%) veterinary samples were submitted for analysis consisting of anthelminthics (175), antibacterials (46), antiprotozoals (8), vaccines (5) and nutritional supplements (5). About 46 % (112) of these samples were obtained from PMS surveys.

Methods

Compendial methods were applied for products with monographs in current versions of the British Pharmacopoeia [19] and United States Pharmacopeia [20]. Alcoholic beverages were

analyzed according to the applicable European Commission (EC) regulation [21]. Where official methods were unavailable, in-house specifications were utilized. All methods were subjected to system suitability tests prior to application. Analyses were performed according to the specific tests requested by the clients.

The various dosage forms received by the laboratory were typically subjected to the tests listed in Table 1. Additionally, PV samples were monitored for related substances and assay as indicators of deterioration, counterfeiting or adulteration.

Table 1: Analytical tests for dosage forms

Dosage form(s)	Analytical tests
Tablets/boli/capsules	Identity, disintegration, hardness, friability, weight uniformity, assay, dissolution
Syrups/suspensions/water-soluble powders	Identity, pH, relative density, assay, microbial load, stability, loss on drying
Injections/infusions/ ophthalmics	Identity, pH, extractable volume, weight uniformity, sterility, assay
Dermatologicals/antiseptics/ disinfectants	Identity, density, pH, content, microbial load
Inhalers/nasal drops	Identity, pH, deliveries per canister, assay, microbial load
Drug substances	Identity, pH, loss on drying, assay, related substances
Ethanol spirit drinks	Identity, pH, total dissolved solids, impurities, assay

RESULTS AND DISCUSSION

Table 2 represents a summary of the results obtained. Detailed data on the samples analyzed are given in Supplementary Table S1.

A total of 1972 samples were analyzed during the 2011-2015 period of which 373 (21.5%) were manufactured in-country, 1543 (78.2%) imported and six (0.3%) indeterminate (Table 2). The latter were PMS samples submitted in loose packs lacking some product details. The low numbers of local products shows a downturn deviation from the trend in the last three decades [11-17]. This situation adds impetus to the Kenyan government's Vision 2030 blueprint and the Big Four Agenda, which aims to enhance the performance of the manufacturing sector, pharmaceuticals inclusive [10]. Hence, a critical analysis of the underlying barriers in achieving these goals is necessary in order to deploy appropriate mitigative measures to enhance local industry.

Compendial methods were applied in analysis of 682 samples (34.6%) distributed among the BP (365), USP (313) and EC standard for alcoholic beverages (4), *in lieu* of which the rest were tested using clients' in-house specifications. Lack of published official specifications may hinder expeditious testing of samples especially those arising from PMS or PV. In-house methods on the other hand, are not publicly available for routine applications. Additionally, they are designed for application in the analysis of specific products with known matrix composition.

Table 2: Quality control results of samples analyzed in DARU during the period 2011–2015

	Body system/ Drug class	Number of samples	Compliant samples		Non-compliant samples	
			Local	Imported	Local	Imported
1.	**Gastrointestinal system**					
	a. Antiulcer drugs	49	5	44		
	b. Anti-emetics	10	1	8		1
	c. Spasmolytics	3		3		
	d. Prokinetics	1		1		
2.	**Cardiovascular system**					
	a. Hemostatics	3		2		1
	b. Thrombolytics	1		1		
	c. Antihypertensives	81	3	78		
	d. Antithrombotics	16		15		1
	e. Vasopressor agents	2		2		
	f. Anti-anginal drugs	3		3		
	g. Hypoglycemic agents	42	9	33		
	h. Hypolipidemics	28	5	21		2
3.	**Eye preparations**	15		15		
4.	**Anti-infectives**					
	a. Antibacterials	613	94	509	1	5
	b. Anthelmintics	213	136	39	35	1
	c. Antiprotozoals	45	12	30	1	2
	d. Mixed anti-infectives	13		12		1
	e. Antimalarials	77	12	56	6	3
	f. Antivirals	21		21		
	g. Antifungals	33	4	28		1
5.	**Nervous system**					
	a. Analgesics	151	17	132		2
	b. DMARDs	2		2		
	c. Anti-inflammatory agents	13	3	9		1
	d. Opioid analgesics	29		28		1
	e. Anti-epileptics	19	1	18		
	f. Psychotropics	26	1	25		
	g. Nootropics	22		22		
	h. Anesthetics	18		17		1
6.	**Musculoskeletal system**					
	a. Anti-myasthenic drugs	1		1		
	b. Muscle relaxants	3		3		
	c. Bisphosphonates	3		3		

	Body system/ Drug class	Number of samples	Compliant samples		Non-compliant samples	
			Local	Imported	Local	Imported
7.	**Endocrine system**					
	a. Thyroid/antithyroid drugs	2		2		
	b. Hormones	7		7		
8.	**Respiratory system**	151	46	99	4	2
9.	**Genitourinary system**					
	a. Erectile dysfunction drugs	23	7	16		
	b. Anti-BPH drugs	12		11		1
	c. Uterotonics	8		5		3
	d. Contraceptives	29		28		1
10.	**Anticancer agents**	38		34		4
11.	**Nutritional products**					
	a. Nutrient mixtures	29	3	24		2
	b. Vitamins	16	1	14		1
	c. Minerals	13	1	12		
	d. Amino acids	2		2		
	e. Electrolytes	15	1	14		
	f. Waters	8	1	7		
12.	**Skin preparations**	32	4	27		1
13.	**Immunomodulatory agents**	5		5		
14.	**Miscellaneous products**					
	a. Antidotes	1		1		
	b. Lozenges	4	1	3		
	c. Antiseptics/disinfectants	4	3	1		
	d. Glycoproteins	1		1		
	e. Herbal products	2	2			
	f. Vaccines	9		9		
	g. Alcoholic beverages	4			3	1
	h. Excipients	1				1
	Total	**1972**	**373**	**1503**	**50**	**40**

BPH – Benign prostatic hyperplasia, DARU – Drug Analysis and Research Unit, DMARDs – Disease modifying antirheumatic agents. All samples (n=6 viz 4 antibacterials and 2 anthelmintics) of unknown origin complied with the tests performed.

The overall non-compliance rate was 4.5%, disaggregated into 11.8% and 2.6% for local and imported products, respectively, indicating a greater non-compliance for locally manufactured products. Nevertheless, these figures represent the lowest failure rate for samples tested in the DARU laboratory since 1980. Notably, about 70% of non-compliance for local products was due to veterinary anthelminthics obtained during PMS. Such non-compliance could be attributed to

non-adherence to current Good Manufacturing Practices (cGMP) by manufacturers and/or weak regulation for veterinary products.

None of the musculoskeletal, endocrine, immunomodulatory and ophthalmic drugs failed in the tests performed. In addition, drugs in the following subclasses complied with their corresponding specifications; anti-ulcers, spasmolytics, prokinetics, thrombolytics, anti-hypertensives, vasopressors, anti-anginals, hypoglycemics, antivirals, DMARDs, anti-epileptics, psychotropics, nootropics, erectile dysfunction drugs, minerals, amino acids, electrolytes, waters, antidotes, lozenges, antiseptics/disinfectants, herbals and vaccines.

Compared to the previous reporting period (2006-2010), the failure rate for anthelminthics increased by 8%, mostly attributable to locally produced albendazole drench samples which failed in the pH and assay tests [17].

Antibacterial drugs recorded the lowest failure rate (1.0 %) since DARU commenced publishing QC reports in 1980 [11-17]. The antibacterial drugs with quality issues originated from PMS including amoxicillin, azithromycin, ciprofloxacin, doxycycline and flucloxacillin. The quality of antibacterials has been of concern due to high failure rates previously encountered, that could promote antimicrobial resistance and predispose the population to treatment failures. Compared to the 2006-2010 period, there was a sharp decrease in non-compliance in antiprotozoals and antifungals. Among 33 antifungal samples analyzed, only one sample of voriconazole tablets failed in the assay and dissolution tests.

The failure rate for antimalarials was 11.7%. The non-compliant samples were mainly artemisinin bulk drug (5/9) which failed the test for related substances (RS) at a threshold of 0.5% w/w. This drug is obtained from *Artemisia annua* leaves through extraction and purification; hence relatively high levels of RS are expected. The remaining non-compliant antimalarials were artesunate-mefloquine, dihydroartemisinin-piperaquine and artemether-lumefantrine, which failed in assay or dissolution tests.

Analgesics recorded high compliance with only two products failing in dissolution while anti-inflammatory steroids had a failure rate of 7.7 % due to assay results for one sample of dexamethasone injection. Among the opioids (morphine injection) and anesthetics (bupivacaine), one sample each did not meet requirements for sterility and pH, respectively.

The respiratory drugs with quality concerns (n = 6, 4%) included ephedrine nasal drops (microbial load), loratadine syrup (pH, assay), montelukast tablets (dissolution) and cough syrups (assay and microbial load).

All the 23 samples of erectile dysfunction (ED) drugs complied with quality tests. This class of drugs gained popularity during the study period with cheap generics becoming readily available. In pursuit for market authorization, several samples of sildenafil and tadalafil were submitted to DARU for analysis, for the first time. Meanwhile, in the anti-BPH category, only one sample of dutasteride-tamsulosin capsules failed in the assay test. Three samples of oxytocin (uterotonic) from pharmacovigilance surveys and one medroxyprogesterone injection (contraceptive) did not comply with assay.

The failure rate of anticancers was 10.5%, including two samples each of cyclophosphamide and doxorubicin which failed in test for RS, pH and assay. These samples were submitted for PV investigation. The results underscore the central role PV plays in quality assurance of critical drugs within the healthcare system.

In the nutritional supplements category, one total peripheral nutrition product failed in the sterility test while one sample of oral capsules showed heavy microbial contamination. Both samples were PV products. One phytomenadione sample did not comply with assay.

All the samples of spirit drinks failed the test for alcohol content. The only sample of excipients submitted (microcrystalline cellulose) did not comply with BP specifications for microbial load.

CONCLUSION

The period under review (2011-2015) recorded the highest number of samples analyzed at the DARU laboratory. This may be attributed to

enhanced testing capacity and surge in the number of samples submitted. The results obtained demonstrate an improvement in the quality performance of the drugs presented, with several critical drug (sub)classes recording no failures. The receipt of PV and PMS samples is notable since it represents a viable approach for QA of drugs in circulation. It would be interesting to review similar reports from the other two accredited laboratories, NQCL and MEDS, to project a complete picture of the Kenyan drug quality landscape.

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Supplementary Materials

Table S1. Details of drug samples analyzed in DARU during the period 2011-2015 (*Supplementary Table S1*).

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