DRUGS AND THE NECESSITY OF ITEMS IN DEVELOPING COUNTRIES

By

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INTRODUCTION

Quality of medicine is a buzz-word. Everybody talks about quality, but most fail to explain what they really mean by it. However, quality is the dimension of output that has the highest impact on consumers, those of pharmaceuticals included.

The Kenyan mass media has over the last two decades, carried reports that question the quality of medicines circulating on the local market. Those concerned allege poor quality, non-efficacious, counterfeits and general lack of adequate policing of the pharmaceutical market. However, there has been no systematic purposive market surveillance of drugs to establish the levels of these problems in the Kenyan market. In my view, similar problems and approaches appertain to other developing countries.

Figure 1: Selected newspaper reports on the poor quality of medicine in Kenya

Although the practice of pharmacy has been in the country officially for over fifty years, the government of Kenya first recognized the importance of regulating the quality of medicines for its citizens in 1977. In that year, the Ministry of Health (MoH) in collaboration with the University of Nairobi (UoN) established the Drug Analysis and Research Unit (DARU), which was housed at the university. The results obtained over a short period were published in 1982 [1]. This opened the eyes of regulators for the need to have better control of medicines in the market. These events together with developments worldwide, led to the establishment of the drug registration (drug market authorization) unit within the Pharmacy and Poisons Board (PPB), the drug regulatory authority, within the MoH in 1982. This unit is charged with ensuring the following activities:

cines circulating in local commerce, and
3. Quality control facilities able to support the two.

Concomitant with technical advancement, it became evident that analytical facilities required expansion and improvement to provide necessary feedbacks and support to the regulators. Improvements of analytical resources at DARU were being outstripped by demand. By 1988, it became clear that DARU capacity could not handle routine sample analysis for registration purposes. The government embarked on alternative development of additional laboratory facilities and a number of feasibility studies ensued. The National Quality Control Laboratory (NQCL) was commissioned in 1994 with the support of the German government (GTZ).

DARU now remains a laboratory within the UoN, and is run by staff of the Department of Pharmaceutical Chemistry. The National Quality Control Laboratory, on the other hand, is under the auspices of the Ministry of Health. The two laboratories have continued to collaborate with each other in terms of consultation and utilization of facilities and equipment. Furthermore, the laboratories share between them the only comprehensive data on quality of drugs in the Kenyan market.

Drug market authorization

Commonly referred to as ôDrug Registrationô it is a process that entails audit of application dossiers for drug registration by a committee of experts. The quality may also be ascertained through testing in the laboratory. This establishes safety, efficacy and quality through an appreciation of general good manufacturing practices (GMP) input to the production of the medicine.

In the initial years, there was limited expertise available to effectively evaluate technical data presented in dossiers to support registration of a drug. For the past 25 years processing of drug marketing authorization has matured and reviews have greatly improved both in terms of expertise and processes. Nevertheless, there still remain technical gaps that need to be filled.

Market authorization, once achieved, allows a medicine to be placed on the market. The consumer identifies with its potency to relieve or heal. In most cases, this spurs production of generics to compete with innovator products. Most worrisome, is that it also attracts counterfeiting. Once a drug is manufactured, the onus is on the manufacturer to supply the regulator with any new information on the product such as new uses and new adverse effects, as well as changes in manufacturing sites, ingredients and processes. In Kenya, the registration of drugs must be renewed every five years. Few manufacturers comply with this requirement.

Since 1982 to date almost 20,000 drugs have been registered in Kenya. The average number of drugs registered annually is about seven hundred. Annually, re-registrations

he total number of registered drugs and those re-
ug products are generics and some are of low quality.

Table 1: Drug Registration in Kenya[a]

Registration status	Number of products
Drugs registered between 1982 to date	19,570
Newly registered drugs in 2007	643
Drugs re-registered in 2007	1,126[b]

[a]Source: Pharmacy and Poisons Board, MoH, Kenya
Data on rejected products was not available.

Drug Quality control

The ability of regulatory body to confirm the quality of a drug product through laboratory testing is a strong statement on the types of medicines on the market within its area of jurisdiction. It acts as deterrence against attempts to offload sub-standard products onto markets.
In Kenya, the quality control functions are carried out by the Drugs Analysis and Research Unit (DARU) and the National Quality Control laboratory (NQCL). The data presented in this paper represents samples analyzed by the two laboratories during the period 1980-2007. In both laboratories, the handling of samples has been similar.

Samples were received from regulatory authorities, local industry, non-governmental organizations, hospitals and private practitioners. The products were either locally manufactured or imported. The drugs were analyzed according to specifications given in the European Pharmacopoeia, the United States Pharmacopoeia or the British Pharmacopoeia [2-4]. Products which are not subject to official compendia were analyzed according to the manufacturerôs methods and specifications.

According to the WHO definition, if a drug, upon laboratory testing in accordance with the specifications it is claimed to comply with fails to meet those specifications, then it is classified as a substandard drug. The term substandard is used to describe the quality status of genuine drugs produced by legitimate manufacturers [5].

Drug Analysis at DARU

Actual drug analysis in DARU started in 1980. By 1989, the initial equipment was obsolete, but none were being replaced. Starting from 1990, the laboratory was supported through a collaborative research project funded by the Vlaamse Interuniversitaire Raad (VLIR). This project was in force in 1994 when the NQCL was launched. Consequently as a means of sustainability, in 1995, the project was reconfigured and continued

epartment of Pharmaceutical Chemistry. The project
nt and transfer of technological know-how.

Since inception, DARU has analyzed 1,882 drug samples. Work has shown that the quality varies with the type of drug, the manufacturer and whether the drugs are locally manufactured or imported. A summary of drug analysis at DARU over almost three decades is given in table 2.

Table 2. Quality Performance of Drugs Analyzed at DARU

	Jan 1980 – Jun 1981	Jul 1981 – Dec 1982	1983 - 1986	1987 - 1990	1991 - 1995	1996 - 2000	2001 - 2005	2006 - 2007
Number of drugs analyzed	182	191	379	127	262	261	379	101
Local drugs (%)	65	65	71	54	59	60	37	24
Imported drugs (%)	35	35	29	46	41	40	63	77
Overall failure (%)	23.1	26.7	31.4	21.6	17.6	21.1	6.1	8.9
Local drugs (% failure)	a	51	46	24	20	25	9	0
Imported drugs (% failure)	a	15	31	20	14	16	5	16.7

a: drugs not categorized into ólocalô and óimportedô during that study period

The overall failure in the period 1980-2000 ranged from 17.6% to 31.4% and dropped to less than 10% in the years 2001-2007. In the period 1980-2000, the locally manufactured drugs were always more (54 to 71%) than the imported drugs analyzed. This trend seems to have changed in the period 2001-2007, when the locally manufactured drugs analyzed were less (below 40%) than the imported ones [6-15]. From 1980 to 2005, the failure of locally manufactured drugs was always higher than that of imported drugs. Surprisingly, in the years 2006-2007, none of the locally manufactured drugs analyzed failed analysis.

In Kenya, like other developing countries some therapeutic categories of drugs are quite important in reducing general sequelae, morbidity and mortality. Results for selected therapeutic categories are shown in Table 3.

of Selected Therapeutic Drug Categories Analyzed at DARU

Therapeutic categories (% failure)	Jan 1980 - Jun 1981	Jul 1981 - Dec 1982	1983 - 1986	1987 - 1990	1991 - 1995	1996 - 2000	2001 - 2005	2006 - 2007
Analgesics	20.0	31.3	9.1	0	0	9.7	a	6.9
Antibiotics	14.9	31.5	30.0	26.2	18.4	10.7	3.2	55.4
Anthelmintics	a	a	14.3	0	25.0	37.5	10.0	3.0
Anti-malarials	-	14.3	6.7	0	23	27.7	26.9	10.9
Antiretrovirals	a	a	a	a	a	28	0	a
Anti-tuberculars	20.0	20.2	a	a	40.0	0	0	a
Dermatologicals	33.0	58.0	56.3	67.7	41.7	25.0	33.3	a
Electrolytes	30.8	45.5	37.8	40.0	14.3	23.1	0	1
Vitamins/ minerals	a	0	40.0	a	83.3	33.3	0	a

a: No drugs were analyzed in this category during that period

The therapeutic classes raising the greatest concern are anti-infective agents, electrolytes, skin preparations and vitamins/ minerals.

In the early 1980s analgesics had a failure of more than 20% but has decreased significantly to below 10%. During the last two decades surveillance has focused more on the anti-infective agents. However, due to the wide use and availability of analgesic products even in the informal sector, there needs to be increased surveillance of analgesics.

Antibiotics have been of concern for the last two decades and especially in the last two years. Except in the 2001-2005, the failure of antibiotics has been high ranging from 10.7 to 55.4%. This trend can be linked with the emergence of resistance aginst the commonly used antibiotics during these periods such as ampicillin, amoxicillin, and co-trimoxazole.

In the tropics, anthelmintics are very important in the prevention and treatment of helmintic infestations. Except for the last two years, failure rates of these drugs have often been high ranging from 10 to 37.5%.

In Kenya, malaria is one of the leading killers, especially among children under five and pregnant mothers. Antimalarials are therefore, a drug category of great concern, as they showed consistently high failure rates. The quality of antimalarial drugs have declined from a 10% failure during 1980-1990 to almost 30% failure during 1990-2005. During this period, the first-line malaria treatment was changed from chloroquine to sulphonamide/pyrimethamine and finally artemisinin combination therapies (ACT), of which the later two have shown high failure rates (up to 35% and 21%, respectively).

gents were not available in public health facilitites in Following global campaigns against multinational companies manufacturing ARVs, the prices reduced significantly thus making the medicines available and accessible to the public in Kenya. This marks the first time that DARU analyzed ARVs. Initially, the failure rate for antiretrovirals was at 28% during the period 1996-2000, but was nil in 2001-2005 [15].

The failure rate of anti-tubercular agents has remained alarmingly high over the three decades (up to 30%). This is a dangerous trend, especially when cases of multidrug-resistant mycobacteria have been reported in Kenya and continue to rise.

The therapeutic classes, electrolytes, skin preparations and vitamins/minerals had failure rates of between 14.3 and 83.3% throughout this period

Drug analysis at NQCL

The drug registration and market surveillance require an operational quality control laboratory devoted to the activities of the drug regulatory authority. In Kenya, this was formally realized by the commissioning of the NQCL in 1994. The take off was slow for the first 10 years. Questions on the quality of ARVs added impetus for the government to re-evaluate the status of the laboratory. Through budgetary allocation and donor funding over the past three years the laboratory has been enabled to replace obsolete equipment and acquire new pieces. In addition, the Ministry of Health has enhanced the human resource capacity to evaluate the increased number of samples the laboratory handles. The laboratory is now in the process of acquiring WHO pre-qualification status.

During the period 1996-2007, the NQCL analyzed 2643 drug samples (Table 4). Most of the samples were analyzed after 2002 with only 107 samples analyzed during the in 1996-2001. The majority of the drugs submitted for analysis were pre-registration samples.

Table 4. Failure Rates (%) of Drugs Analyzed at NQCL

	1996-2001	2002-2003	2004-2005	2006-2007
Number of drugs analyzed	107	442	1139	955
Local drugs (%)	41.0	40.0	27.2	28.2
Imported drugs(%)	59.0	60.0	72.8	71.8
Overall failed drugs (%)	30.8	27.1	12.6	15.0
Local drugs failure (%)	22.7	32.0	18.7	23.8
Imported drugs failure (%)	34.9	23.9	10.4	11.5

The overall failure in the period 1996-2003 ranged from 27.1% to 30.8% and dropped to 12.6% in the years 2004-2005 before rising slightly in 2006-2007 to 15.0%. In 2002 a post market surveillance exercise on antimalarials was carried out by Welcome Trust, as result of which 62 samples were submitted to the NQCL for analysis. Further, in 2004, a post distribution surveillance exercise conducted by the Kenya Medical Supplies Agency

or analysis. Consequently the total number of samples igher compared to the previous years. In 2006, the Pharmacy and Poisons Board in collaboration with the WHO conducted a countrywide survey on anti-malarials, thereby submitting 42 samples to the laboratory.

Throughout the period under consideration the imported products formed the bulk of samples analyzed (59-73%). The failure rate among the imported products was higher during 1996-2001 but this trend took a turn around in subsequent years being about 10% lower than the locally manufactured products.

Although NQCL largely analyses pre-registration samples from the Pharmacy and Poisons Board and DARU gets samples from a wider range of sources, the results obtained from the two laboratories are largely similar and the same categories of drugs exhibit high failure rates as shown in table 5.

Table 5: Failure Rates (%) of Selected Therapeutic Drug Categories Analyzed at NQCL

Therapeutic categories (% failure)	1996-2001	2002-2003	2004-2005	2006-2007
Analgesics	50	16.7	12.3	17.5
Antibiotics(Antibacterials)	24.3	19.9	9.4	17.3
Anthelmintics	0	33.3	17.9	10
Antimalarial drugs	14.3	38.8	20.6	13.8
Antiretrovirals	a	12.8	3.4	2.9
Antitubercular drugs	30	38.9	46.5	17.4
Electrolytes	16.7	0	25	0
Vitamins/minerals	a	0	36.7	25

a: No drugs were analyzed in this category during that period

The failure rate for analgesics was very high in 1996-2001 (50%). This drastically dropped to 12.2 - 17.5% in subsequent years. Unless the failure rate comes down to the single digit level, the quality of analgesics remains a major concern.

During the period 1996-2001 the failure rate for antibiotics was 24.3%. This gradually reduced to 9.4% in 2004-2005 before rising again to 17.3% in 2006-2007.

The failure rate for anthelmintics was high (33.3%) in 2002-2003, but has dropped gradually to 10% in 2006-2007.

Antimalarials had a failure rate of 14.3% during the period 1996-2001. This increased sharply to 38.8% in 2002-2003, probably due to the market surveillance products analyzed in 2002. The high rate of failure in 2004-2005 may also be attributed to the same reason. The majority of the non-compliant products were the

ch mainly failed in the dissolution test of

The initial failure rate for antiretrovirals was 12.8% (2002-2003), which later dropped sharply and was sustained at 2.9-3.4%. These results are in agreement with those obtained in DARU and depict an impressive quality of the antiretrovirals under circulation in Kenya. Since 2001, ARVs are under compulsory licensing manufacture following passing of the requisite parliamentary bill and are provided to the patients for free at designated centres. The tight distribution chain plays a big role in limiting substandard products and counterfeits.

The failure rate of antitubercular agents was consistently high during the period 1996-2005. The exceptionally high failure recorded in 2004-2005 may be due to the samples from market surveillance handled at the time.

In similarity with DARU work, high failure was periodically observed for electrolytes and vitamins/minerals.

Counterfeit products

A counterfeit medicine is defined by WHO as ña medicine which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging.ò [5].

Data already enumerated show a significant rate of failures. Amongst the failures are a number of counterfeit medicines. In Kenya, there has been no systematic way of identifying counterfeit drugs. Such drugs are encountered in the course of quality control, while others can be traced in the market after reports of poor efficacy or by observation

The latest finding was the antimalarial dihydroartemisinin-piperaquine tablets which contained no piperaquine. Others have involved sulphamethoxypyrazine-pyrimethamine, zidovudine-lamivudine and amoxicillin-clavulanate tablets that contained no sulphamethoxypyrazine, lamivudine and clavulanate potassium respectively. Samples of corticosteroid creams were found to have no active ingredients, while raw materials purported to be amoxicillin and caffeine had no active ingredients. The data obtained shows that the majority of counterfeit products encountered in DARU and NQCL were antimalarial drugs and antibiotics.

The earliest counterfeit medicines encountered were skin preparations (table 6). The driving force behind dermatological steroidal counterfeits, is the high level of abuse by women who use these skin preparations as skin lighteners.

dermatological preparations

Year	Labeled API	Found API	Other Parameter	Comments
1988	Hydrocortisone	Hydrocortisone acetate	-	Two products
1988	Hydrocortisone acetate	Hydrocortisone	-	One product
1995-2000	Dermovate® cream (clobetazole)	None	Packaging counterfeited	-

Panadol® (paracetamol) is the most counterfeited analgesic (table 7). This brand enjoys good market performance in Kenya as an over the counter medicine (OTC), which entices the counterfeiting.

Table 7: Counterfeit analgesics

Year	Labeled API	Found API	Other Parameter	Comments
2000	Panadol® junior tablets (paracetamol)	Aspirin	Packaging counterfeited	-
2005	Panadol® tablets (paracetamol)	Paracetamol	Packaging counterfeited	Passed assay test

Prior to 2006, the sulfadoxine/pyrimethamine drugs were the first line antimalarials. Thereafter, the ACTs were moved to the first line treatment. Counterfeiting has followed the same trend since the first line antimalarials tend to have high demand and market turnover. Table 8 is a record of the counterfeit antimalarial products encountered in DARU and NQCL.

Table 8: Counterfeit Antimalarial medicines

Year	Labeled API	Found API	Other Parameter	Comments
2004	Sulphamethoxy-pyrazine + Pyrimethamine	Pyrimethamine only	-	Failed assay
2007	Metakelfin® tablets (sulphamethoxy-pyrazine + pyrimethamine)	Pyrimethamine only	Packaging counterfeited	Failed in assay and dissolution
2007	Duo-Cotecxin® tablets (dihydro-artemisinin + piperaquine)	Dihydro-artemisinin only	Packaging counterfeited	Passed assay

The antiretrovirals could be attributed to the tightly controlled supply chain. This practice has greatly helped in controlling the development of resistance to antiretrovirals. Only one product was encountered as shown in table 9.

Table 9. Counterfeit Antiretroviral medicines

Year	Labeled API	Found API	Other Parameter	Comments
2003	Zidovudine/ Lamivudine	Zidovudine	-	Passed assay

Among, the antibiotics, amoxicillin and co-amoxiclav are the most counterfeited products (table 10). These products are the most popularly prescribed as first line antibiotics in the primary healthcare facilities and therefore have an established market thus making it attractive towards counterfeiting.

Table 10. Counterfeit antibiotic medicines

Year	Labeled API	Found API	Other Parameter	Comments
2004	Amoxycillin trihydrate (raw material)	None	-	-
2004	Amoxycillin + Clavulanate tablets	Amoxycillin only	-	-
2006	Amoxil™ 500 mg capsules (Amoxycillin)	Amoxycillin	Packaging counterfeited	Product failed dissolution and assay

Other counterfeit products encountered included methylated spirit, caffeine and prednisolone (table 11). The underlying factors for the counterfeiting of these products are not clear.

Table 11: Other Counterfeit Products

Year	Labeled API	Found API	Other Parameter	Comments
1983	Methylated Spirit (Ethanol)	Methanol	-	-
2004	Caffeine	None	-	-
2007	Prednisolone tablets	None	Packaging Counterfeited	Different tablet sizes

healthcare system are quite devastating. Use of the counterfeit medicines leads to treatment failures, mortality and resistance to anti-microbial agents. Indeed the antimalarials and antibiotics comprise majority of the counterfeited products. These products are fast sellers in the developing countries thus making them targets for counterfeiting. Dealers in this category of products take advantage of the loopholes in the surveillance systems of the drug regulatory authority. Enhance vigilance by the drug regulatory authority and systematic market surveillance are the strategies that need to be instituted to curb circulation of counterfeit products.

Market surveillance

Marketing of medicines assumes that the quality presented in the technical dossier and quality control of the actual products, are continually consistent. This has been proven not always to be the case.

In addition, there are an unknown number of unregistered drugs in the Kenyan market, many of which are substandard and some are counterfeits. Due to the high number of products in the market and constraints in the inspectorate department, errant manufacturers and/or distributors are often not apprehended

Drug regulatory authorities find it difficult to enforce quality standards in a market laden with corruption, lack of adequate personnel for inspection, poorly equipped and understaffed quality control facilities and non-deterrent sanctions. Profligate generics and parallel importation, compound the problem.

In developing countries where drug imports are customs and duty free, a less vigilant regime is always the norm. Anybody who is legally allowed to possess medicine can import them. In Kenya this window has been exploited by unscrupulous people to deal in counterfeit drugs.

Conclusion

The failure rates still remain unacceptably high, especially with anti-infective agents, which have serious implications in development of multi-drug resistance and treatment failures. Surveillance of counterfeits still remains poor and many cases still go undocumented due to low vigilance. There is need for stepping up market surveillance through infrastructure development and capacity building in the country.

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