Quality Assurance and Safety issue of Pharmaceutical Products marketed in Developing countries

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Hiermit versichere ich, dass ich diese Arbeit selbständig und ohne jede unerlaubte Hilfe angefertigt habe, dass diese oder eine ähnliche Arbeit noch keiner anderen Stelle zur Prüfung vorgelegen wurde.

Ort, Datum Ndjamawe Bah-Traore

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In memorial of my very dear mother Nmaa Azia Arietu Mendeh and father Dadja Hadj Shafiou Djibril BAH-TRAORE, your Souls are honored and your Names remain forever.

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Abbreviations

ACT:	Artemisinin Combination Therapy
ADDO:	Accreditation of Drug Dispensing Outlet
ADR:	Adverse Drug Reaction
API:	Active Pharmaceutical Ingredient
ARV:	Anti-Retroviral
BP:	British Pharmacopoeia
CAMEG:	Central d´Achat des Médicaments Essentiels Génériques et dispositif Médicaux
CRS:	Chemical Reference Substance
DRA:	Drug Regulatory Authority
DPLM :	Direction des Pharmacies Laboratoires et consommable Médicaux
DGPLM :	Direction Générale des Pharmacies Laboratoires et du Médicament.
cGMP :	current Good Manufacturing Practices
ECOWAS:	Economic Community of West African States
EMRA:	ECOWAS Medicines Regulatory Agency
FDB:	Food and Drug Board
GCP:	Good Clinical Practices
GDP:	Good Distribution Practices
GFATM:	Global Fund for Aids Tuberculosis and Malaria
GHS:	Ghana Health Service
GLP:	Good Laboratory Practices
GMP:	Good Manufacturing Practices

GPHP:	Global Pharma Help Fund
GSP:	Good Storage practice
HIV:	Human Immunodeficiency Virus
HMM:	Home Medicines Management
ICH:	International Conference on Harmonization of Technical requirements for the registration of medicinal products for Human Use
IP:	International Pharmacopoeia
IFPMA:	International Federation of Pharmaceutical Manufacturers Association
IFM:	International Monetary Fund
LCS:	Licensed Chemical Shops
MEDS:	Mission for Essential Drugs Supply
MQAS:	Model Quality Assurance System
MRA:	Medicine Regulatory Authority
NAFDAC:	National Agency for Food and Drug Administration and Control
NDRA:	National Drug Regulatory Authority
NMR:	Nuclear Magnetic Resonance
NGO:	Non-Governmental Organization
NMRA:	National Medicine Regulatory Authorities
OOS:	Out-Of-Specification
OTC:	Over the Counter
PCN:	Pharmacist Council of Nigeria
PICs:	Pharmaceutical Inspections Cooperation Scheme

PMV:	Patent Medicine Vendor
POM:	Prescription Only Medicines
POS:	Point Of Sale
PQM:	Promoting the Quality of Medicines
PSI:	Population Service International
PSP:	Pharmacie de la Santé Publique
QA:	Quality Assurance
QC:	Quality Control
SOP:	Standard Operating Procedure
SP:	Sulphdoxine Pyrimethamine
UEMOA:	Union Economique et Monétaire Ouest Africaine
UNFPA:	United Nations Population Fund
UNICEF:	United Nations Children's Fund
WAHO:	West African Health Organization
WAEMU:	West Africa Economic and Monetary Union
WHO:	World Health Organization
XRPD:	X- Ray Powder Diffraction

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Abstract

The circulation of substandard medicines remains a serious problem in the resource limited countries like Sub-Saharan Africa, where most of the drugs available are imported. Medicines sold in these markets are frequently found to have ingredients at concentrations that are too high or too low. They tend to contain impurities and poor quality ingredients. They are also often labeled inadequately. There are a number of reasons for these shortfalls. For example, many medicines that are manufactured for export to developing countries are not regulated to the same standards as those for domestic use. Most Sub-Saharan countries lack adequate regulations for ensuring the safety and efficacy of their medicines. Porous borders between the countries in the region facilitate the illicit importation of drugs and drugs piracy. We surveyed a selection of drugs available in six of the 15 countries that make up the Economic Community of West African States (ECOWAS) to gauge the extent of, and the main reasons for, the circulation of substandard drugs in Sub-Saharan Africa. The six countries were Benin, Burkina Faso, Côte d´Ivoire, Ghana, Nigeria and Togo. This dissertation describes the survey and its outcomes. It also considers what needs to be done on the regulatory front to improve the quality and safety of medicines in the region. Free trade and globalization policies have led to an anarchical invasion of poor quality medicines into the markets of developing countries. Nigeria has the biggest medicines market in the ECOWAS region, where there are very high activities in cross-border and parallel trade in pharmaceuticals.

Medicines in the ECOWAS region can be purchased from pharmacies and other outlets. Drugs for sale can be found exposed in bowls or trays along the streets and in market stalls or carried on the head by itinerant hawkers[*]; all these practices are carried out under inappropriate climate conditions. In addition, product-packaging standards vary across markets, and prescription recommendations and contraindications also may differ. Differences in product packages remove the familiar packaging clues that are so important in the visual detection of counterfeits. Price differentials create an incentive for drug diversion within and between established channels. There is a lack of effective intellectual property protection and due regard is not paid to quality

[*] Hawkers: Medicine sellers who wander along streets and from house to house.

assurance. Retailers may use formal as well as informal channels and some studies have reported significant quantities of smuggled drugs in shops including in batches labeled for exclusive hospital use. With drugs entering through porous borders, safety warnings and product recalls are more difficult to execute. With the exception of Nigeria and Ghana, drug regulation is not a national health policy priority in many West Africa countries. Documentation collected during our survey of the national medicine agencies from the six ECOWAS countries illustrated that, while on paper there are rules governing the pharmaceutical sector, the implementation of said rules in practice is weak due to a lack of political will.

This study is aimed at evaluating the regulatory flaws and some quality parameters of the most commonly used essential drugs. The results will be useful to the ongoing drug registration harmonization process and especially to the West African Health Organization (WAHO) in developing appropriate intervention strategies to ensure that only effective drugs are allowed on the ECOWAS market and to promote the public confidence in the quality of the medicinal drugs. This will contribute to the implementation of the Essential Drugs Concept as envisaged in the WHO guidelines. Also, to further the findings explored in the previous papers on substandard and counterfeit medicines, in particular by broadening the scope of our research to include the necessity to transcend the linguistic barrier and duplication of effort (WAEMU*/ECOWAS) in regional harmonization of drug registration and related regulation, processes and laws governing medicines marketing. As a result, this will form an important supplement appeal for awareness to what has already been explored in previous publications.

In our survey, internet searches using Google scholar and PubMed formed the first level of our inquiry. We used search terms related to medicine sellers in developing countries and to substandard medicines. Between January and March 2010, we purchased, without prescriptions, 68 treatment packs and blisters of antibacterial agents and an antimalarial from various types of drug outlets, i.e. pharmacies, market stalls, drug stores and itinerant hawkers on the street and at bus stations. All collected medicines would have been prescription-only products in Western

* WAEMU: West Africa Economic and Monetary Union, the 7French speaking countries in the ECOWAS region.

markets. The purpose of our purchase was not disclosed to any of the sellers. The drugs were then transported in a sealed black nylon bag to the final field testing location in Germany to determine the quality assurance range. They were kept under ideal conditions: stored at ambient temperature, in low humidity and away from sunlight.

Primary screening of the samples was conducted using X-ray diffraction at the Institute of Pharmacy, University of Bonn.

Secondary screening of the samples was conducted using near infrared Raman spectrometry (from ServanTech in Frankfurt). In the absence of reliable results from X-ray diffraction and Raman spectrometry due to restricted facilities and the non-availability of comparator samples (in six cases), with which to confirm the spectrum results, we screened the products using the Global Pharma Help Fund's mobile mini-laboratory, GPHF-Minilab. GPHF-Minilab screening was based on the related protocol for disintegration, which awards products a "pass" if they disintegrate within 30 minutes.

We also performed High Performance Liquid Chromatography (HPLC) analyses at the Institute of Pharmacy and Food Chemistry at the University of Wuerzburg. The assay methods were designed to yield additional information such as the content of active ingredient per unit dose, the presence of residual starting materials from synthesis and the principle drug decomposition products. This was expected to provide additional information on the quality and safety of the analyzed drugs.

We also performed a visual survey (outer packaging and packaging leaflet) of all purchased

68 packs and blisters.

Table 1 provides an overview of the results of our analyses.

Overall, we found that:

87 % (59/68) of samples had obvious labeling errors;

20 % (1/5) of samples failed disintegration tests;

20% (1/5) of samples failed thin layer chromatography;

20% (1/5) of samples failed X-ray diffraction; and

6% (1/16) of tested samples failed NIR Raman spectrometry.

HPLC detected labeled active ingredients in all samples; except for one amoxicillin sample (the substance to be examined(X_3) was not soluble in the mobile phase. Table7). Six of the nine doxycycline samples did not comply with the requirements of the European Pharmacopoeia. Their contents were found to be above the 95-105% acceptance limit of declared active ingredient. The highest deviation found was 162.19%. The variation of content above the limit of 105% may be due to bad manufacturing methods. Unknown HPLC peaks, especially in the doxycycline measurement, may have been caused by the beginning of degradation (epimerization, dehydration, inactivation by means of reactions due to used excipients).As a non-pharmacopoeial method was used for analysis; the results have to be regarded with caution. Differences found in the amounts of active ingredients may also be due to bad manufacturing habits (inaccurate weighing, capsules filling) or bad storage conditions either by the manufacturer, exposition on market stalls, or during transportation. Most of the drugs we collected were manufactured in India.

Our survey revealed that, it is more likely that the drugs we assessed were substandards, as a result of bad manufacturing practices by the company exporting the products and the absence of well-established drug regulatory bodies in importing countries, rather than as a result of fraudulent manufacturing. Though our findings do not exclude counterfeiting, we did not find a single sample in which the labeled active substance had been replaced by another ingredient. Our conclusion, that the drugs were less likely to be substandard because of counterfeiting, is also based on observations in the field and our discussions with local regulators and manufacturers in the surveyed countries. Manufacturing deficiencies included incorrect labeling, illegible package leaflet and outer packaging with an incomplete address of the manufacturer. Unknown impurities were found in some of the products. Storage conditions in the surveyed countries themselves – such as open market stalls or hawkers carrying medicines under the sun – may have also played a part in facilitating the deterioration of active ingredients. The huge involvement of unqualified persons in the procurement and distribution of drugs in the surveyed countries is likely to be another major reason for the circulation of substandard medicines. While the sample size in this survey is small, it gives an indication about the availability of substandard antibiotics in the ECOWAS region.

Weak regulatory systems in the ECOWAS countries and inefficient border controls call for a regional harmonization of drug regulation. Stricter regulatory rules would compel exporters from

countries with established drug regulatory systems to make sure that their export to developing countries are of the same high quality as those that they register in their own countries. Drug regulation would also go some way towards stopping imports of low-quality/counterfeit drugs from other little-regulated markets.

Establishing means to provide a clearer distinction between counterfeits and substandard medicines in the ECOWAS countries may help to enhance the general pharmaceutical quality management system within the framework of a new regulatory approach; public education; and dialogue and persuasion before litigation and other punitive measures are implemented. Also, trying to convert hawkers and illegal traders to other lucrative activities may be an alternative. The ECOWAS region needs to establish adequately equipped and resourced laboratories for drug analysis and quality control. Such laboratories should be supported by WHO prequalified quality laboratories and other inter-country and inter-regional networks. It appears that when suppliers are aware that the quality of their products is being subject to continuous monitoring, they make sure that they export drugs that are of good quality (Figure 10).In addition, a pharmacovigilance plan needs to be developed in the ECOWAS region as part of the overall medicines regulatory system. Boosting regulatory enforcement in the ECOWAS region would be beneficial in terms of improving the packaging, labeling and the chemical quality of medicines. Efforts to develop a harmonised regulatory framework in the ECOWAS region have already been undertaken. In the context of the African Medicine Regulatory Harmonization Initiative, ECOWAS is planning to establish a regional co-ordinating medicines registration harmonisation board called the ECOWAS Medicines Regulatory Agency (EMRA). It is expected that EMRA would provide technical assistance to member state national medicines regulatory authorities and register critical products for public health interventions within the ECOWAS region.
New provisions to control manufacturers, wholesalers and importers should be established. Attacking the problem through multiple routes will be the most effective way to combat the problems of substandard and illicit marketing of drugs.

The attainment of quality assurance for medicines in the ECOWAS region should be accelerated. The WHO prequalification program, health institutions and donators should emulate the West Africa Health Organization (WAHO) in supporting local human capacity building in medicines regulatory issues and local pharmaceutical manufacturers through technical and financial assistance. The ultimate aim is to help promoting the import of only high quality medicines and the domestic manufacture of drugs according to the principles of good manufacturing practice. We hope that our survey will increase awareness of the circulation of poor quality medicines in

Sub-Saharan Africa and encourage regional harmonization of drug regulation in particular in the ECOWAS region.

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PART 1: INTRODUCTION

Pharmaceutical markets are distinguished by a number of key features (Scherer 2000)[1]. First, drugs are divided into prescription-only and over-the-counter products, with many restrictions on the availability of the former. Secondly the demand for pharmaceuticals is generally inelastic, reflecting the predominance of a high willingness to pay for medicines. Thirdly, research and development costs are relatively high and lastly, patent protection plays a very important role in profitability. A frequently observed phenomenon is the "generic competition paradox" which occurs when, following the expiry of a patent, generic alternatives enter the market, but the originally patented brand continues to be sold at a higher price (Scherer 2000)[2]. Medicine markets in developing countries are mostly generic markets. The main difference between the life cycles of originator and generic medicines is found in the development phase. While for originator medicines the focus is on safety and efficacy data (proven in preclinical and clinical trials), generic medicines are assumed to be safe and efficacious if they can demonstrate pharmacokinetic parameters similar to the originator product. For generic medicines the focus essentially lies on quality aspects.

Markets play an extremely important role in the distribution of pharmaceutical products in developing countries. There is some overlap with other terms frequently used, such as parallel markets which arise to evade price, quality and quantity controls in one hand, and black markets, which refer to illegal trade (Jones, Lindauer and Roemer 1991)[3]. By contrast, in developing countries the sector remains dominated by small-scale retailers, and there are many ambulatory sellers, and periodic markets. Pharmacists and pharmacies are relatively rare. (Table12)

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[1] Scherer, F.M. 2000. "The Pharmaceutical Industry." in Handbook of Health Economics, Volume I, edited by A.J. Culyer and J.P. Newhouse: Elsevier Science B.V; available from http://www.kemri wellcome.org/dissertations/Phd_2004_Goodman_C.pdf .Internet accessed on July 23th, 2011.

[2] Scherer, F.M. 2000. "The Pharmaceutical Industry." in Handbook of Health Economics, Volume I, edited by A.J. Culyer and J.P. Newhouse: Elsevier Science B.V; available from http://www.kemri-wellcome.org/dissertations/Phd_2004_Goodman_C.pdf .Internet accessed on July 23th, 2011.

[3] Jones, C., D.L. Lindauer and M. Roemer (1991) „Parallel, Fragmented, and Black: a Taxonomy." in Markets in Developing Countries, edited by M. Roemer and C. Jones. San Francisco, California: ICS Press; available from http://www.kemri-wellcome.org/dissertations/Phd_2004_Goodman_C.pdf.Internet accessed on July 26th, 2011.

Generic pharmaceuticals represent almost two-thirds of total sales in developing countries and branded generics are much more important than unbranded generics in sales, their manufacturing is predominantly for the home market. Cultural and behavioural patterns also have a key bearing on the consumption of medicines. Although pharmacies are scarce in most rural and some suburban areas, they represent the main source of non-prescription medicines for most people, provided the shelves are well-stocked. As a result, a great deal of self-diagnosis, self-medication and re-use of prescriptions occurs. This gap is often maintained or even gets wider over time. There are essentially two markets or market segments: one of price insensitive consumers, willing to pay high prices for the original brand, and another consisting of price sensitive consumers willing to shift to generics (Suh et al. 2000)[4]. Price insensitivity in the first group may arise because established products have built up accumulated goodwill and reputation during the patent period. Higher prices may also be maintained because consumers lack information about generics, because they are concerned about the quality of newer products, or because prescribers and patients are not directly affected by the financial consequences of their drug choice (Ferrandiz 1999)[5]. In developing countries, spending on medicines comes largely from household resources (table 12) and prescribed medicines have to be paid out of pocket at the time the person is ill. Price differentials create an incentive for drug diversion within and between established channels; there is a lack of effective intellectual property protection; and due regard is not paid to quality assurance. Parallel trade in pharmaceuticals generates a number of monitoring difficulties which may pose significant threats to public safety. With drugs entering through porous borders, safety warnings and product recalls are difficult to execute. In addition, product-packaging standards vary across markets, and prescription recommendations and contradictions also may differ. Differences in product packages remove the familiar packaging clues that are important in the visual detection of counterfeits.

[4]Suh, D. C., W. G. Manning, Jr.S. Schondelmeyer, and R. S. Hadsall. "Effect of multiple-source entry on price competition after patent expiration in the pharmaceutical industry." Health Service Res. 2000 June; 35(2): 529–547; available from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1089132. Internet accessed on August 8th, 2011.

[5]Ferrandiz, J. M. 1999. "The impact of generic goods in the pharmaceutical industry." Health Econ 8:599-612; available from http://www.kemri-wellcome.org/dissertations/Phd_2004_Goodman_C.pdf.Internet accessed on July 26th, 2011.

Parallel trade results in unregulated distribution pipelines and weakened regulatory control of the supply chain, both of which are characteristics that facilitate counterfeiting and substandard drugs. Although practically all types of pharmaceutical products have been shown to be involved, the existing data suggest that anti-infectious agents, particularly antibiotics and antiparasitic agents are the most counterfeited products in developing countries[6].

The essential medicines list, first assembled by a World Health Organization (WHO) expert panel in 1977 and revised every two years to reflect current health challenges, is an inventory of medicines which address pressing local/regional health needs. Medicines are identified through an evidence-based process and quality, safety, efficacy and cost-effectiveness are key selection criteria. In close cooperation with national regulatory agencies and partner organizations, the Prequalification Programme aims to make quality priority medicines available for the benefit of those in need at affordable price. This is achieved through evaluation and inspection activities, and by building a national capacity for sustainable manufacturing and monitoring of quality medicines. Literature related to pharmaceutical products in developing countries predominantly addresses concerns about the lack of effective drugs and their high cost, through discussion of the role of essential drugs policies, patent law, and incentives for research and development for neglected diseases[7]. Few studies have examined drug quality[8,9] and have investigated poor quality drugs in terms of the correct amount of active ingredient. This paper focuses on quality assurance in procurement and distribution channel.

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[6]WHO. Counterfeit Drugs: Guidelines for the Development of Measures to Combat Counterfeit Drugs. Geneva: WHO; 1999. p. 1-60; available from http:// www.jac.oxfordjournals.org/content/60/2/214.full; Internet accessed on March 22th, 2010

[7] Essential Medicines List; available from http:mednet3.who.int/prequal/default.htm. Internet accessed on April 11th,2010

[8] Mrazek, M.F. and E. Mossialos. 2003. "Stimulating pharmaceutical research and development for neglected diseases." Health Policy 64:75-88; available from http://sphweb02.umdnj.edu/sphweb/sphc/programs/outreach/documents/Politics of Medication Access in Developing Countries.pdf .Internet accessed on July 26th, 2011.

[9] Binna Onwujekwe , Harparkash Kaur, Nkem Dike, Elvis Shu, Benjamin Uzochukwu , Kara Hanson, Viola Okoye and Paul Okonkwo. Quality of anti-malarial drugs provided by public and private healthcare providers in south-east Nigeria; available from http://www.malariajournal.com/content/8/1/22. Internet accessed on August 12, 2011.

PART 2: BACKGROUND INFORMATION AND LITERATURE REVIEW

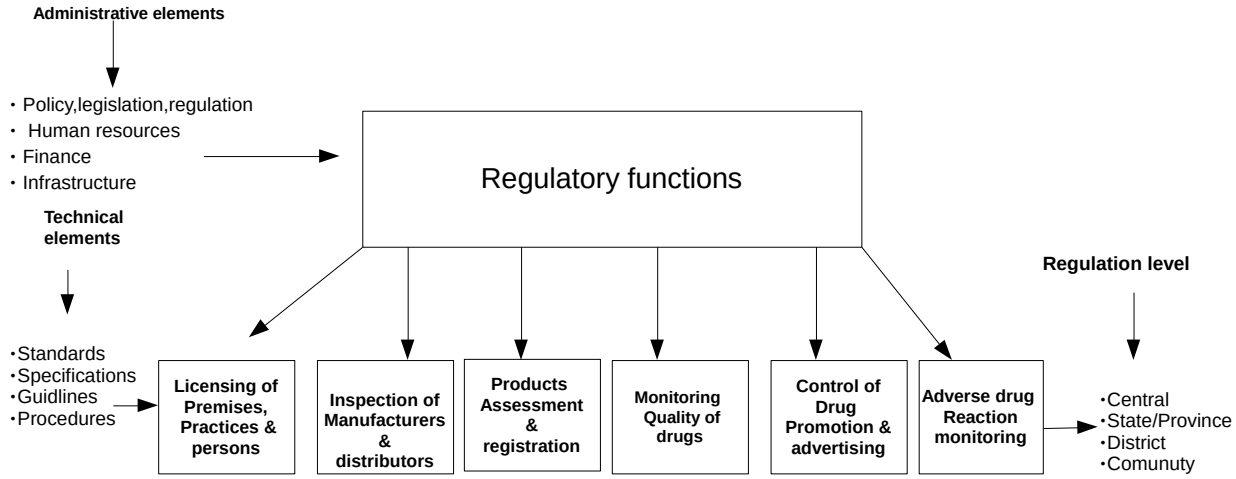
CHAPTER I: Regulatory Aspects of Medicines in Sub-Saharan Africa

This chapter gives an insight of the problems of quality assurance globally and within the surveyed ECOWAS region as well as the preliminary Literature Review. The rationale of the study is discussed along with problem analysis and recommendations. It brings the reasons and importance of the study (pooling technical and human resources through regional harmonization) into focus.

1.1. Functions in the Regulation of Medicines

The administrative elements of drug regulation carry out the regulatory functions which include licensing of premises, human resources and practice, inspection of manufacturers and distributors, product registration and assessment, enforcement, quality control of drugs and public awareness. The relevant legislation will specify the requisite qualifications (and sometimes also the number) of personnel handling specific tasks, the procedures used to produce, import and distribute pharmaceutical products and the health and safety conditions of the premises in which any of these processes take place. The manufacturing, importation and distribution premises are inspected to ensure compliance with regulatory specifications. The technical elements form the major requirements to be followed. Every activity in the regulatory functions is expected to be carried out efficiently on all levels within a country. Guidelines set out the conditions, content, format of applications, and the detailed technical requirements against which dossiers will be assessed based on international guidelines. The framework allows for a comparison of drug regulation between countries. Drug regulation can spill over from one country to another; the drug policy in one country can affect another as the knowledge of what happened in one country can help another prepare for similar challenges in future. To provide credible regulatory services, National Medicines Regulatory Authorities (NMRAs) must have specific measures in place to avoid conflict of interest in decision-making, to make their rules and decisions transparent. Regulation is traditionally seen as the use of bureaucratic and administrative controls by governments to correct market failures. Without adequate policy, human resources, finances and infrastructure, drug regulation will fail. The framework below (Figure 1) reflects the building blocks comprising the regulation of medicines. The level of regulation indicates the level at which the various regulatory functions are undertaken. The political structures of a country determine the overall governance of drug regulation. Medicines regulation is a public policy that restricts private sector activities in order to attain social goals.

Figure 1 Framework showing key components of drug regulation



Source:Sauwakon Ratanawijitrasin, Eshetu Wondemagegnehu
World Health Organization 2002 WHO Library Cataloguing-in-Publication Data ISBN 92 4 156206 4

Source: Ratanawijitrasin S. Wondemagegnehu E, (2002) Effective drug regulation- A multicounty study. A book published by WHO Library Cataloguing-in-Publication Data ISBN 92 4 156206 4.Document accessed in Cotonou Benin on September 22, 2011.

Every regulatory function contributes to ensuring the safety quality and efficacy of drugs. The action taken by the authority should cover all drug regulatory functions in a balanced fashion. The regulatory process should be systematically monitored in order to identify problems and determine whether actual activities match the intended actions. Governments are responsible for carrying out regulatory functions to ensure that all drugs on the market are of acceptable quality, safety and efficacy. A most basic question is whether drug regulation achieves its declared aim, which is protection of the public from ineffective, unsafe, or inadequately tested drugs. Moreover, the drug regulatory agencies should become a learning organization which routinely conducts self-assessment and continuous quality improvement. Peer review by drug regulatory authorities in other countries can serve as a mean of external auditing, whereby the performance of one agency can be compared with that of its peers. Drug Regulatory Authorities (DRA) should communicate regularly with their client. We emphasize that no guidance can cover all eventualities, and common sense and a clear focus on the needs of the regulatory authority are

the best guides. Educating citizens about the efficacy, safety, quality and rational use of drugs will ultimately enhance the achievement of regulatory objectives.

1.2. Quality Assurance of Pharmaceutical Products

Quality assurance of pharmaceuticals is a major public health challenge, particularly in the light of growing cross-border health issues and the international dimension of trade. In many developing countries, an unfortunate combination of two factors exists. On the one hand, there is predominance of imported finished products and on the other, a lack of adequate analytical services and appropriate human resources. The movement of pharmaceutical products in international commerce necessitates various safeguards on the part of importing countries and institutions to assure that pharmaceutical products are safe, effective, and of adequate quality when received by their final consumers. Quality assurance of pharmaceutical products is based on a reliable system of evaluation and registration to establish safety, efficacy, and confirmation through inspection that the manufacturing conditions fulfill requirements for Good Manufacturing Practices. Quality assurance of an imported product would ideally include:

i) Registration of the product in the country of manufacture;

ii) Approval of manufacturing conditions by pharmaceutical inspection of the manufacturing plant;

iii) Licensing of the product in the country of importation

iv) Pharmaceutical quality analysis of a batch of the product by the manufacturer's laboratory before the product is released;

v) Additional analytical testing should be done to confirm that the batch received did not deteriorate during transit.

Such an ideal set is practically rare in developing countries where technical tools and financial resources to set-up national quality assurance systems are not easily available. Due to political, social and cultural affiliations, markets show substantial regional differences in availability and promotion of drugs. This variation depends on affluence, health requirements, capacity for the local manufacturing, and the restrictions which countries may impose, to control any dangerous or inappropriate use of drugs. Because of the limited number of industrial plants, the majority of developing countries import most of their drugs, and transnational corporations are adept at

exploiting variations in such markets. Commercial interests may conflict with public health needs in developing countries, particularly when people are poisoned[10,11]due to inadequate restriction of pharmaceutical use, misleading advertising or inappropriate labeling.All finished drug products should be identified by labeling, as required by the national legislation, bearing at least the following information:

- the name of the pharmaceutical product;
- a list of the active ingredients (if applicable, with the International Non-proprietary Names (INNs)), showing the amount of each present, e.g. number of dosage units, mass or volume;
- the batch number assigned by the manufacturer;
- the expiry date in an un-coded form; the directions for use, and any warnings and precautions that may be necessary;
- the name and address of the manufacturer and the responsible for procurement and distribution.

Quality assurance of medicine plays a major role in ensuring that medicines intended for human use meet the minimum requirements or specifications. The National Drug Regulatory Authority (NDRA) in a country where a drug is produced is responsible for evaluating and registering the drug, inspecting and licensing manufacturing premises. The NDRA is also responsible for controlling import and export agents, distributors, wholesalers and retailers; and overseeing quality control. Quality assurance is of crucial importance for the success of treatment programs; medicines manufactured below established standards of quality can lead to therapeutic failure, development of drug resistance and toxic or adverse reactions. The pharmaceutical substance, formulation and dosing of any drug for human use are typically described in a monograph

[10]Singh J et al. Diethylene glycol poisoning in Gurgaon, India, 1998.Bulletin of the World Health Organization, 2001, 79(2):88-95.Ref No.99-0329; available from www.who.int/bulletin/archives/79(2)88.pdf.Internet accessed on September 12th, 2011.

[11]Fake meningitis vaccine in Niger (editorial).Scrip, 23 August 1996, 2157:12; available from http://apps.who.int/medicinedocs/en/d/Js2300e/16.3.Internet accessed on September 13, 2011.

published in the internationally accepted Pharmacopoeia. These monographs provide the specifications and standards against which independent quality control testing can be verified, and will be important in the quality assurance process.

1.3. Safety issues of Medicines

Medicines cure infectious diseases, prevent complications from chronic diseases, and alleviate pain. With higher sales rates occurring through non-regulated outlets, the retailers of medicines in less resourced countries are an important source of disease treatment. Retailers increase the accessibility, the range and reliability of drug stocks, but several marketing failures were evident. There is a high occurrence of parallel distribution, information on treatment quality is poor, and negative externalities arise from inappropriate drug use. These failures contribute to the use of ineffective medicines, under-dosing, and inequitable access to quality care. While some patients use just one treatment source, referring to multiple providers is common, and patients may combine modern and traditional remedies during one illness- episode. Another widespread issue is poly-pharmacy, where providers prescribe unnecessary drugs. For example, rates of antibiotic use during fever episodes often vary with unclear justification.

Drug legislation assigns two types of responsibility to drug regulatory authorities: the authority to assess pharmaceutical products thus determine whether they should be registered, and the authority to monitor and change the information and registration status of a drug after marketing approval through the pharmacovigilance or post market surveillance. However, the regulation is more oriented to pre-marketing assessment than to post-marketing review. Registered products are rarely reevaluated. Yet even if pre-marketing assessment has been thoroughly conducted, it may not be sufficient to guarantee the efficacy and especially, the quality of a drug throughout its entire lifecycle. Emphasis should be placed on post-marketing surveillance. Parallel trade in pharmaceuticals generates a number of monitoring difficulties that are not readily apparent but pose significant threats to safety and quality. With drugs entering through various channels safety warnings and product recalls are difficult to execute.

Where the pharmacovigilance system is weak or non-existent; a high degree of responsibility is placed on medical staff to guard against adverse effects. Such informal surveillance is often compromised by the acute lack of healthcare staff in most developing countries, where medicines are often prescribed to patients by health auxiliaries who only receive a very short and basic training that does not emphasize the detection of drug side effects. Moreover, many toxic

side effects are difficult to detect by clinical observation. For example, the rise in temperature often observed after post-surgery administration of intravenous fluids is usually interpreted to reflect a general degradation of the patient's condition, but we have noted instances where this is in fact the result of a poor manufacture of the intravenous fluid resulting in contamination with pyrogens. In addition patients often have to travel long distances to receive medication and can rarely afford the time or financial cost of remaining under hospital supervision. Because individual treatments are frequently ineffective, multiple treatments sought during the course of an illness episode sometimes result in cumulative over-dosing.

Governments' failures were also evident in the form of a poor quality in public health sector treatment, and the absence of an efficient enforcement of regulatory laws. Sesay[12]investigated the use of expired essential drugs including Chloroquine (CQ) in Sierra Leone, and the attitudes of medical practitioners to the subject matter. The author reports that there were variations in the shelf life of CQ products audited, ranging from 3 to 5 years. More worrying, 67% of practitioners estimated that expired products could be used despite their diminished efficacy; 27% of health practitioners in this study stated categorically that expired products should not be used.

Rather than being passive recipients of care and advice, consumers take an active role in the choice of outlets, and in some cases, choice of treatment. Treatment seeking takes place within a pluralistic health system, encompassing health facilities in the public, non-governmental organization (NGO), community health workers, traditional healers and retailers (Williams and Jones 2004)[13] .Many studies found that people very often tend to begin with home treatment, and then proceed to the national health center when home treatment strategies were perceived to have failed[14]although home treatment remains an important option at all stages of illness. Drug shop

[12] Sesay MM. Expiry dates on pharmaceuticals-some worrying realities in Sierra Leone. International Pharmacy Journal.1994; 8:202–206; available from www.ncbi.nlm.nih.gov/pmc/articles/PMC2653781. Internet accessed on April16th, 2010

[13]Williams, H. A., and C. O. Jones. 2004. "A critical review of behavioral issues related to malaria control in sub-Saharan Africa: what contributions have social scientists made?" SocSci Med 59:501-23; available from http://www.biomedcentral.com/1472-698X/9/26; Internet accessed on April27th, 2010

[14]Nyamongo, I. K. 2002. "Health care switching behaviour of malaria patients in a Kenyan rural community."SocSci Med 54:377-86; available from www.ncbi.nlm.nih.gov/pubmed/11824914; Internet accessed on Juni 15th, 2010.

visits can be distinguished in a sub-set of household surveys, which show that buying drugs from retailers is generally very common. The median percentage of using drug shops during acute childhood illness is roughly 50%, although results range from 15% to 82% across various studies[15]. In Togo for example, only 20% of children less than 5 years of age with fever were conducted to a health center during their illness, while 83% were treated at home with an antimalarial, obtained from a street or market vendor[16]. A study in Kenya found that most mothers purchased drugs from retail outlets within one day of noticing the symptoms of childhood malaria, but the average time lag before a public health facility is reached, was 3 days[17]although prompt appropriate treatment is rare. However, since some studies have shown that early treatment of childhood fever with ineffective drugs may results in severe outcomes[18], it is important to emphasize that in the case of persisting fever, caregivers should seek regulated health services in time for proper diagnosis and management. There is some evidence that home treatment reduces the time to obtaining care[19]. On the other hand home treatment may lead to incorrect diagnosis, and administration of inappropriate dosages in the case of persisting disease. Another consequence is a possible delay in seeking appropriate diagnosis and treatment.

[15]Brieger, W. R., A. Unwin, G. Greer, and S. Meek. 2004b. Interventions to improve the role of informal private providers in malaria case management for children in Africa: BASICS II and the MalariaConsortium; prepared for The Malaria Case Management Working Group, Roll Back Malaria; available from http:/ / www.rbm.who.int/ partnership/ wg/ wg_management/ docs/ medsellersRBMmtgsubcommitteereport. pdf];Internet accessed on July 24th,2011

[16] Deming, M.S., Gayibor, A., Murphy, K., Jones, T.S. &Karsa, T. (1989) Home treatment of febrile children with antimalarial drugs in Togo. Bull World Health Organ. 1989; 67(6): 695–700; available from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2491321/ pubmed; Internet accessed on January13th,2011

[17]Aly Théra, M., D'alessandro, U. Ouedraogo, A., Packou, J., Ahmed Deida Souleymane, O., Fané, M., Ade, G., Alvez, F. and Doumbo, O. (2000), Child malaria treatment practices among mothers in the district of Yanfolila, Sikasso region, Mali. Tropical Medicine & International Health, 5: 876–881. doi: 10.1046/j.1365-3156.2000.00652; available from http://www.ncbi.nlm.nih.gov/pubmed/11169277 ;Internet accessed on September 11th,2011.

[18]Orimadegun, A.E., Amodu, O.K., Olumese, P.E. &Omota, O.O. (2008) Early home treatment of childhood fevers with ineffective antimalarials is deleterious in the outcome of severe malaria. Malaria Journal 7:143; available from http://www.malariajournal.com/content/7/1/143;Internet accessed on March 22nd, 2009

[19] Hamel, M.J., Odhacha, A., Roberts, J.M. & Deming, M.S. (2001) Malaria control in Bungoma district, Kenya: a survey of home treatment of children with fever, bed net use and attendance at antenatal clinics. Bulletin of World Health Organization, 79, 1014-1023; available from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2566703/pdf/11731808.pdf; Internet accessed on January 27th,2012

This may have severe implications for diseases like Plasmodium falciparum malaria in which late diagnosis and therapy can lead to cerebral forms of the disease and high fatality rates.

The WHO defines appropriate treatment of childhood fever as receipt of an antimalarial within 24 hours of symptom onset (WHO & UNICEF 2003).It is increasingly recognized that in order to improve the majority of treatments for many common health problems, governments have to look beyond the public sector and, acknowledge the reality of the widespread retail sector use, and address the ways in which policy intentionally and unintentionally influences private sector behavior (WHO 1998). The retail sector has been largely ignored, with initiatives generally limited to poorly implemented regulation. Problems relating to drug safety (and efficacy) are generally due to the use of drugs containing toxic substances or impurities, drugs whose claims have not been verified or which have unknown severe adverse reactions, substandard preparations or counterfeits. All of these problems can be tackled effectively only by establishing an effective drug regulatory system. Guaranteeing the safety, efficacy and quality of drugs available to the public is the main goal of drug regulation, and encompasses a variety of functions. Key functions include licensing of premises, persons and practices; inspection of manufacturing facilities and distribution channels; product assessment and registration (marketing authorization); Adverse Drug Reaction (ADR) monitoring; Quality Control (QC); control of drug promotion and advertising. Each of these functions targets a different aspect of pharmaceutical activities, but all of them must be undertaken simultaneously to ensure effective consumer protection. Moreover, no studies have used a regulatory framework to analyze the retail market for health care in West Africa (ECOWAS), although such a framework is likely to be well-suited to improving quality assurance and address safety issue. This paper is intended to address this gap in knowledge.

CHAPTER II: Overview of the Pharmaceutical Environment

2.1. Pharmaceutical Sector Environment in Surveyed Countries

Developing countries are mainly located in three continents namely: Africa, Asia, and South-America. The pharmaceutical challenges show similar patterns across all of these countries. A survey of all those regions is unrealistic and even surveying a single continent lies outside the scope of this thesis. Sub-Saharan Africa alone is a huge batch; due to the allocated time and financial limitations, it has been possible to survey six countries from the economic community of West Africa states (ECOWAS) namely Benin, Burkina Faso, Cote d´Ivoire, Ghana, Nigeria and Togo. The political reality in these countries significantly influences policies, practices, business activities as well as pharmaceutical sector.The major problem encountered in this study was the initial reluctance of regulatory bodies to divulge vital information thus revealing their level of performance.

Economic Community of Western African States (ECOWAS)

Source: http://mapsof.net/map/map-of-ecowas; Internet accessed on December 2011

The Economic Community of West African States (ECOWAS) was established in May 1975 by the treaty of Lagos. The region covers a total area of 5,079,400 km² with a population of about 268 million. Half of the ECOWAS´ population is located in Nigeria and its economy dominates the region. ECOWAS has a need for quick access of quality essential medicines due to its disease burden. In general, the region suffers under the burden of Malaria, Tuberculosis, neglected tropical diseases and other newly emerging diseases (diabetes and cardiovascular

disorder). In addition to these communicable and non-communicable diseases, poverty and malnutrition have also an impact on the types of medicines required.ECOWAS is a regional institution grouping fifteen countries (including the eight WAEMU [West Africa Economic and Monetary Union] member countries): Benin, Burkina Faso, Cape Verde, Côte d'Ivoire, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Niger, Nigeria, Senegal, Sierra Leone and Togo. Each member of the Economic Community of West African States (ECOWAS) is a multisource (generics) importer of pharmaceuticals. The climate in all member countries corresponds to Class IV tropical climate according to the International Conference on Harmonization (ICH) classification (Grimm, 1998)20.Until early 1980´s the pharmaceutical sector in most ECOWAS member countries was monopolized by national agencies. The procurement, handling and distribution of medicines were under the control of national pharmaceutical distribution agencies which generally were supplied by the previous colonial metropolis and the traceability was simple. The scale of poor quality medicines was very low and limited to rural areas where national healthcare service was not available. During 1980´s the quasi total countries of West Africa had to introduce structural adjustment programs and reforms recommended by the International Monetary Fund (IMF). In the health sector, one of the results of implementing the reforms was increased participation of the private sector in the importation of pharmaceuticals, without a parallel increase in the capacity of technical means and human resources to institute effective quality assurance measures. For more than 50 years of existence, countries like Cape Verde, Guinea, Gambia Sierra Leone, and Togo have no efficient quality control laboratory[*]. During my survey in the Economic Community of West Africa (ECOWAS) countries, I witnessed how decadence pharmacy profession is in term of regulation; many people prefer purchasing medicines in the market than pharmacies, so that they can get affordable prices. For instance, in visited five drug stores only one (20% of vendors at drug stores) in Ouagadougou knew the correct dose of Sulfadoxin in Artemisin; this reveals that employees in some official

[20] Grim V. Extension of the International Conference on Harmonization: Tripartite guidelines for stability testing of new drug substances and products to countries of climatic zones III and IV. Drug Dev. Ind. Pharm. 24: 313-325. Drug Development and Industrial Pharmacy (1998) Volume: 24, Issue: 4, Pages: 313-325 PubMed: 9876591;Abstract;available from www.ncbi.nlm.nih.gov; Internet accessed on January 24th,2012

* Personal Information from WAHO Training on GMP-Inspection for National Medicine Regulatory Authorities and local Pharmaceutical Manufacturers in ECOWAS region in PRAIA -Cape Verde March 2011.

pharmacies have no basic pharmaceutical education. Medicines can be purchased in general stores, kiosks, market stalls, formal pharmacies and also from itinerant hawkers. The survey countries (Benin, Burkina Faso, Cote d'Ivoire, Ghana, Nigeria and Togo) face considerable challenges in ensuring that available medicines are safe, of acceptable quality and efficacious. Most of the illicit sellers ignore that under the local climate conditions their medicines are readily degraded, some rely exclusively on the expiration date printed on blisters to ensure the quality to the consumer. Like most resource-limited countries, ECOWAS (Economic Community of West Africa States) depends largely on importation to response to medical needs of their populations. Drug registration is a pre-requisite for purchase in resource-limited countries, but authorization to register a medicine is often granted on the basis of a simple review of documents. Quality is impossible to assure in the absence of proper controls that at minimum, include verification of information submitted for evaluation through site inspections, review of batch documentation, and random analysis of drugs supplied (European Commission Humanitarian Aid Department2006)[21]. Drugs manufactured for export are often not regulated to the same standard as those manufactured for domestic use in exporting countries. The purchasing power for pharmaceuticals in these countries is very low, most importers and distributors of pharmaceuticals tend to pay more attention to low prices rather than to the quality. They source their imports from the cheapest suppliers. Suppliers of pharmaceuticals to a market characterized by such a low purchasing power as in Benin, Burkina Faso, Cote d´Ivoire, and Togo rely on cheap brands, as low prices are favorable to the general population. With such a large difference in prices one would be interested to know if those brands are pharmaceutically equivalent. In addition, the free substitution of one brand to another is practiced on the assumption that those dosage forms which contain the same amount of active ingredient are equivalent. It is a known fact that the bioavailability of generic identical drugs might shift[22]. The outcome of such variations may have serious therapeutic implications, especially for drugs with a narrow therapeutic index (aminoglycoside antibiotics) and a steep dose response curve. It is reasonable to discourage substitution between different brands/generics, unless the necessary measures have

[21]Review of Quality Assurance (QA) Mechanisms for Medicines and Medical Supplies in Humanitarian Aid. European Commission Humanitarian Aid – Concept Paper, Brussels; available from www. ec.europa.eu/.../drugs_quality_concept_paper.pdf. Internet accessed on March 15th,2011.

[22]http://www.crazymeds.us/pmwiki/pmwiki.php/MedInfo/BrandNameVsGenericMedications.Internet accessed Feb, 8th, 2012.

been taken to show that the products are equally effective in delivering the medicament to the systemic circulation.

In an environment of multi-source importation, market preference for cheaper brands and lack of quality control facilities, the trade in substandard / counterfeit drugs is likely to flourish, rending the quality assurance of drugs on market a challenging problem. Moreover, the confidence of health workers and patients in the health system is easily eroded when there are reports (even when they are unsubstantiated) of substandard drugs in circulation. Prescribers overwhelmed by the multitude of brands, (some of which are perceived to be of poor quality) may prefer the use of expensive brands as they associate good quality with high price. This may negatively influence the achievements made through the efforts by the governments to increase access to safe, effective and affordable medicinal products to the majority of their citizens.

Since its foundation in 1975, the West African economic organization has no harmonized information available on the quality of drugs marketed in ECOWAS region and there is neither a WHO-prequalified quality control laboratory nor a prequalified local manufacturing plant in the region. It is therefore important to encourage local pharmaceutical manufacturers to upgrade their facilities as well as to improve on human resource capacity and technology to increase the production of quality medicines. This will contribute to the implementation of international accepted Quality standard in manufacturing (Good Manufacturing Practice) and distribution (GDP: Good Distribution Practice). Coincidentally, the linguistic differences are also reflected in the systems of procurement and distribution of medicines, production, marketing, and contribute to the challenges facing medicines registration and the harmonization of regulations as a public health tool for improving accessibility, affordability and availability of safe, efficacious and quality medicines in the region.The West Africa Health Organization (WAHO) was formed in 1987 by a protocol, which grants the WAHO official status as a specialised agency of all the

15 ECOWAS countries.The driving force behind the WAHO's creation was the incongruence of the agendas that were being pursued by the two inter-governmental health organizations that existed in the region at the time. These were the Francophone "Organisation de Coordination et de Cooperation pour la Lutte Contre les Grandes Endemies" (OCCGE) and the Anglophone West African Health Community (WAHC). It was felt that, as matters of health are not bound by linguistic differences, it would benefit the people of the region to synchronize the activities of the two organizations and combine resources to enhance the impact of their programs in West Africa. The OCCGE and WAHC therefore merged to form the WAHO, an organisation

committed to transcending linguistic barriers in the region to serve all the 15 ECOWAS Member States. Since then, communication and information exchange between member countries have improved tremendously and has made integration easier and more beneficial to all Member States. Currently a consensual draft of ECOWAS harmonized regulation on quality of drugs marketed in West Africa is delayed by the hesitation from the French speaking countries´ group (UEMOA: Union Economique et Monetaire Ouest Africaine). To my view, this hesitation seems to be a manipulation from foreign pharmaceutical partners. This study is aimed at evaluating some quality parameters of the most commonly used essential drugs. The results will be useful to the ongoing harmonization process and especially to the West African Health Organization (WAHO) in developing appropriate intervention strategies to ensure that only effective drugs are allowed on the ECOWAS market and to promote the public confidence in the quality of the medicinal drugs. This will contribute towards the implementation of the Essential Drugs Concept as envisaged in the WHO Prequalification Program. This study is significant because the people's right to health includes the right to access a reliable standard of healthcare and assurance that drugs received are not only genuine but safe, effective, and affordable.

2.2. Analysis of the Drug Situation in Nigeria

With a population of around 167 million Nigeria represents a large market for drugs. Whatever happens in Nigerian pharmaceutical market has an impact on medicinal products circulating in the ECOWAS markets. "Theoretically the Nigerian industry has a capacity to cover between 50 – 75% of the nation's drug needs. However, the actual production lies below 30% thus 70% of all drugs on the Nigerian market are imported." (Okoli, 2000)[23]. In Nigeria, the National Agency for Food and Drug Administration and Control (NAFDAC) has enlarged the scope of counterfeit drugs to include drugs without the full name and address of manufacturers, drugs labeled "For Export Only", expired and relabeled drugs with the intention of extending their shelf lives, drugs containing banned substances and drugs not registered by NAFDAC. NAFDAC focuses too much on registration and not enough emphasis on regulating the distribution system. Fake drugs

[23] Erhun W.O, Babalola O.O, Erhun M.O. Drug Regulation and Control in Nigeria: The Challenge of Counterfeit Drugs: Journal of Health & Population in Developing Countries; 2001, 4(2):23-34; available from http://www.nigeriapharm.com/Library/Drug_regulation.pdf ; Internet accessed February 2nd, 2012.

were first noticed in Nigeria in 1968, as the situation deteriorated, Nigeria was rated as the country with the highest incidence of fake drugs in 2001. A study in 2001 that assessed the content of drugs from pharmacies in Nigeria revealed that around half of the preparations had concentrations outside the upper and lower limits of the pharmacopoeia applicable in the region from which they originated. Consequently, made-in-Nigeria drugs were banned in other West African countries. The issue of fake drugs and others is assuming new dimension as to who is responsible or not for averting the situation. NAFDAC has appointed analysts in India – which is a major exporter of medicines to Nigeria – who now certify drugs before they leave India for Nigeria. For imported products from all countries, the Nigerian medicine agency now requires mandatory pre-shipment information to be provided by importers. The Agency (NAFDAC) also held a summit with Indian authorities, in order to sensitize and convince them to help Nigeria by stopping exportation of substandard drugs to the country. It held another one in conjunction with House committee on Health with ambassadors of the countries identified as the root of the influx of fake drugs to the country like India, Indonesia, China, Pakistan, and Egypt; a position was reached that they will help Nigeria in addressing the issue.

2.2.1. Pharmaceutical Regulation

Amongst the regulatory bodies are: (i) The National Agency for Food and Drug Administration and Control (NAFDAC), (ii) The Pharmacists Council of Nigeria and (iii) Federal Task Force on Counterfeit and Fake drugs, these are the three bodies relevant to the study. NAFDAC was established by decree 99 of 1993, this decree regulates and controls the production, importation, exportation, advertisement, use and sale of all drugs, processed food, cosmetics, medical services, including all drinks, chemicals and so on. NAFDAC is established to:

- conduct appropriate tests and ensure compliance with standard specifications designated and approved by the council for the effective control of quality of food, drugs, cosmetics, medical devices, and their raw material as well as their production processes in factories and other establishments;

- undertake appropriate investigation into the production premises and raw materials for food, drugs, cosmetics, medical devices, and establish relevant quality assurance systems, including certification of the production sites and of the regulated products;

- undertake inspection of imported food, drugs, cosmetics, medical devices, and establish relevant quality assurance systems and of the regulated products;

- grant authorization for the import and export of narcotic drugs and psychotropic substances as well as other controlled substances;

- collaborate with the National Law Enforcement Agency in measures to eradicate drug abuse in Nigeria.

Recently, official signing of NAFDAC green page was done to ensure only registered and reliable drugs were allowed to be used in hospitals, pharmacies and others health establishments. With NAFDAC green pages all stakeholders in the industry obtained a legitimate common ground, where their products and services would be show-cased to Nigeria and the world, through three media; the book form which will be in volumes and yearly, compact disks and via an established internet homepage. NAFDAC has improved screening of drugs in the field; it has undertaken forensic analysis of low quality drugs and pursued those selling and marketing them. Screening has improved with the deployment of several small portable laboratories, known as Global Pharma Health Fund e.V. Minilabs® for rapid product screening where formal laboratory facilities are sparse. NAFDAC is also conducting a survey and audit of all drugs on sale in order to build a pharmaceutical database. From 2002, drug failures fell to roughly 16% in 2006 and are now down to about 10%*. NAFDAC is pushing further by being the first anti-counterfeit department in the ECOWAS region to deploy six hand-held laser (Raman) spectrometers, which can provide immediate authentication of drugs. This deployment is helping to close down more of those locations still selling fake products. Despite the achievement, NAFDAC has no power to prosecute all offenders connected with faking or manufacturing of substandard drugs, anybody arrested with such activities and taken to the court will not be prosecuted in shortest period due to the court procedure.

The Pharmacist Council of Nigeria(PCN) as a body in charge of determining the standard of knowledge and skill to be attained by person seeking to become registered member of pharmacy profession, has tried to establish a mandatory registration which would be required prior to practicing as a pharmacist. This would ensure that quack members (to some extent) are given no room to practice as they are polluting the profession and render it unprofessional. The council is not functioning as it is expected in determining who practices pharmacy in Nigeria.

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* According to the director-general of NAFDAC, Dr. Paul Orhii (Personal communication, February 25, 2010)

Section 11 subsection A of PCN act, states who shall be entitled to be a pharmacist, "such a person should be of good character, fit and proper; has attended a course of training approved by the council, or the course was conducted at an institute approve by the council; hold a qualification approved by the council; and has undergone the statutory continuous internship training for not less than one year under a registered pharmacist…"

The non-regulatory bodies include (i) The Pharmaceutical Society of Nigeria, (ii) Nigeria Association of General Practice Pharmacists, (iii) Nigerian Association of Industrial Pharmacists, and (iv) The Pharmaceutical Manufacturers Group of the Manufacturers Association of Nigeria (PMG/MAN).

2.2.2. Drug Distribution Chain in Nigeria

The drug distribution network in Nigeria is in a state of chaos because it consists of open markets, patent medicine stores, and community pharmacies managed by NGOs (Non-Government Organizations), private and public hospitals, wholesalers/importers and pharmaceutical manufacturers. It is a common scene in Nigeria to see medicinal product traders who sell cigarettes, kola nuts, and oranges, among other items, in market kiosks, car parking wards, and road sides hawking drugs that range from over the counter items to antibiotics. The medicines are usually left under the sun in such conditions that could facilitate the deterioration of the active ingredients.

Patent medicine stores are owned by the holders of a patent and medicine vendor license. Ordinarily patent medicines should be sold in their original packs. Over the Counter (OTC) drugs are the only drugs authorized to be sold by the vendors but they generally sell all types of drugs as determined by their financial capability. People have taken the Pharmacy profession for granted as if it does not require any skills and training before a person becomes a pharmacist. Patients prefer to go to the market[s] directly than pharmacies, so that they can get affordable prices and in turn, the drugs they buy often are fake, expired or poor quality. These kind of episodes do occur daily and the patients do not know, because they are after cheaper drugs (due to countries´ socioeconomic conditions), nevertheless they are being cheated in most cases with either expired or fake drugs. In order to maximize their profits pharmaceutical companies prefer

to distribute their products via unregulated markets instead of using official routes such as hospitals or pharmacies. Thus the drugs may end up in the hands of unqualified personal.

NAFDAC has therefore; enforced a sustained surveillance at all selling outlets. Lists of identified fake / substandard products are published in Nigerian newspapers and medical revues on a routine basis.(Annex 1).The World Health Organization (WHO) has agreed to NAFDAC's plan to carry out a Pan – Nigerian survey to determine the extent of substandard products in circulation. New guidelines have been put in place to ensure the importation of genuine drugs into Nigeria; these are:

- Before the registration or renewal of registration of any product, NAFDAC inspectors must inspect the production plants in the exporting country. In the case of drugs, the factory must be 'WHO certified', to ensure Good Manufacturing Practice.

- In the future, before drugs are imported into Nigeria even after registration, NAFDAC approved analysts in the respective countries must conduct a pre-shipment analysis of the drugs[24].

2.3. Analysis in other Countries (Benin Burkina Faso, Cote d´Ivoire, Ghana, Togo)

The nature and size of pharmaceutical activities in a country determine the type and burden of responsibility which the Drug Regulatory Authority (DRA) must bear. Benin Burkina Faso, Cote d´Ivoire, Ghana and Togo adopted the WHO guidelines for inspection but do not carry out routine inspections abroad mostly due to financial constraints. Thus they have to rely on certification and documentation from "well established regulatory authority from abroad. The Ghana Food and Drug Board now carries out constant routine inspection of both foreign and local production plants; the inspected firms are responsible for inspection fees before and after drug registration, this will give them a better overview of activities of drug manufacturers[25].

[24] www.nafdacnigeria.org/drug-testing Internet accessed on November 23rd, 2011.

[25]Ratanawijitrasin S. Wondemagegnehu E, (2002) Effective drug regulation- A multicounty study. A book published by WHO Library Cataloguing-in-Publication Data ISBN 92 4 156206 4.Document consulted in Cotonou Benin on September 22, 2011.

Pharmaceuticals trade and professional groups exist in Nigeria and the rest of five countries surveyed. Consumer groups have also been formed in these countries. However, their influence in relation to drug regulation functions is unclear. The quality of medicines varies greatly, particularly in low-income countries, because of poor manufacturing and various uncertainties in the distribution system. Regulatory gaps identified in Benin, Burkina Faso Cote d´Ivoire and Togo are, the neglected informal sector for medicines supply, over-concentration on pre-market rather than post-market monitoring, more attention given to inspection of manufacturing practice than of distribution channels. New legislation that imposes GMP standards on domestic companies should be implemented rigorously. Standard requirements should be introduced for all distributors and registered retail outlets supplying pharmaceuticals in the National healthcare system.Visual assessment procedures for accepting medicinal products should follow the steps outlined below.

Examine the products (individual treatments), checking for:

a. Condition of the containers for the integrity of the primary and secondary packaging

b. Check the overall labelling of the primary packaging, secondary packaging and any patient information leaflets for spelling mistakes and damage

c. Check labels for manufacturing and expiry dates

d. Check contents for shape and colour consistency

The outcome of these should be documented and stored and will also help to guide the sampling process for laboratory testing.

The particularity in Ghana is that there were no street vendors along main streets where the government started a program for Accreditation of Drug Dispensing Outlet (ADDO)[26]. Through this initiative, unlicensed drug vendor are licensed, regulated and trained to understand basic

[26] Segre J, Tran J (2008). What works: Care Shop Ghana (Improving access to essential drugs through conversion franchising; available from www.nextbillion.net/resources/casestudies. Internet accessed on September 25th,2011.

pharmacy ethics in order for them to provide better services to their consumers. Ghana Food and Drugs Board in collaboration with the USP's Promoting the Quality of Medicines (PQM) set up a quality monitoring surveillance programme in multiple locations across Ghana. USP is a scientific non-profit organization that develops globally recognized standards for the quality of medicines. Through the PQM program, USP works in developing countries to help verify and improve the quality of medications intended to treat life-threatening neglected diseases such as malaria, HIV/AIDS and tuberculosis. Several cases of falsified antimalarial medicines without any active substance have been reported in the recent years[27]. Consequently, the PQM programme incorporates quality assurance in its medicine regulatory mechanism, but still counterfeiters and grey importers of substandard medicines use unofficial channels to outwit the existing system. In this context, Ghana's Food and Drugs Board (FDB) uses GPHF-Minilabs for routine drug quality testing with fully-fledged confirmation analysis to improve post marketing monitoring. Market monitoring in Ghana is funded by the Medicines Transparency Alliance (MeTA) and till to date, two studies of antibacterial, and antidiabetic drug testing have been conducted. In both studies, all products tested passed for presence of active pharmaceutical ingredients and did not involve counterfeiting. Product failures were however reported in specific reference to test of potency (assay of indicated active ingredient) and dissolution in both studies. Necessary regulatory interventions to address the problems were implemented.

The findings underscore the need to maintain collaboration to build Ghana's national medicines quality assurance infrastructure in the interest of public health and safety. In 2009 the same PQM (Promoting the Quality of medicines) program uncovered a counterfeit version of Novartis' Coartem® a widely used antimalarial. A citizen´s alert notified the authorities after suspecting the drug he bought might be faked[28]. The discovery of the counterfeits in use at a government-run hospital, private clinic, and distributed through many pharmacies has resulted in a nationwide recall of all thirteen drugs, including publicizing the names of the outlets where they were found. This is intended as a strong deterrent, making pharmacy and hospital

[27]Global Pharma Help Fund latest news December 2011; available from WWW.gphf.org. Internet accessed on December 23rd, 2011.

[28]Substandard and counterfeit antimalarial drugs discovered in Ghana Provided by US Pharmacopeia, posted by News Desk Report on November 9th, 2010.

procurement personnel more vigilant about their suppliers. The fact that the fake and poor quality drugs were so widespread in many areas across Ghana and in many types of outlets shows the need not only for continuing surveillance but also for active enforcement of anti-counterfeiting laws.

In Togo, there is a necessity for a greater emphasis on public awareness of the problem of substandard medicines, law and regulations enforcement on the distributors and local manufacturer, in line with internationally-recognized standards, with tough, prohibitive sanctions on those who fail to comply.

The conclusion is that substandards are widespread and also that they affect countries differently. The specific problems each individual country has to tackle will depend on the regulatory, cultural, and socio-economic policies of that country. As such, some problems can be addressed easily, while others require hard thinking, large resources, and national or even international cooperation. Substandards are extremely hazardous to the public health since patients consider them to be genuine and valid for consumption. The risk to the patient is significant, since substandards can have serious adverse health effects and clinical outcomes[29].This underlines the importance of drug regulatory agencies whose role is to prevent substandards from reaching the market and to remove those which are already there. Good Manufacturing Practices (GMP) is the standard used by regulators to prevent substandards to reach the distribution chains. GMP, as defined by the WHO, demands "*that products are consistently produced and controlled to the quality standards appropriate to their intended use", whilst "diminishing the risks inherent in any pharmaceutical production*"[30]. Quality evaluation primarily provides important information on the drug content and secondly identify the cause (if any) of the poor quality. Thus simple, rapid and inexpensive assays are necessary to easily set up an on-site quality control unit before

[29]Green MD. Antimalarial drug resistance and the importance of drug quality monitoring. J Postgrad Med [serial online] 2006 [cited 2012 Feb 3]; 52:288-90; available from: http://www.jpgmonline.com/text.asp?2006/52/4/288/2815. Internet accessed on Jan9th, 2012.

[30]World Health Organisation (2007). Quality Assurance of Pharmaceuticals, A compendium of guidelines and related materials, Volume 2, 2nd edition, p. 17; available from www. apps.who.int/medicinedocs/documents/s14136e/s14136e.pdf.Internet accessed on Mai 20th,2011.

large-scale quality evaluation can be performed by a reference laboratory (Green et al. 2001)[31]. In ensuring this, the WHO helpfully provides assistance as to guidelines and principles for effective GMP. In addition, other important standards set by the WHO include Good Distribution Practices (GDP) and Good Storage Practices (GSP). National medicines regulators make such standards a mandatory requirement when assessing dossiers for marketing authorisation. A 1999 report by the WHO found that more than 40% of low income countries had no laws regarding the manufacturing and distribution practices of pharmaceuticals, nor did they have inspections of facilities carried out by regulatory representatives[32]. GMP ensures the quality of a product throughout the whole production process and is not the control of the finished product.The quality of drug packaging is key to ensuring that the medicines arrive safely in the hands of the patient for whom they are intended.It is not in the interest of the consumer if a product that has been produced according to GMP is later stored and distributed under adverse conditions. Where a drug is repackaged to improve compliance, the quality of the approved packaging should not be jeopardised. Interaction between packaging and drug is possible due to the multiplicity of container components and active pharmaceutical ingredients as well as solvents used in a variety of dosage forms. The quality of the packaging of pharmaceutical products plays a very important role in preserving the stability, quality and efficacy of the drug. It must:

a. Protect against all adverse external influences that can alter the properties of the product, e.g. moisture, light, oxygen and temperature variations;

b. Protect against biological contamination;

c. Protect against physical damage;

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[31] Green MD, Mount DL & Wirtz RA (2001) Authentication of artemether, artesunate and dihydroartemisinin antimalarial tablets using a simple colorimetric method. Tropical Medicine and International Health 6(12), 980–982; available from http://onlinelibrary.wiley.com/doi/10.1046/j.1365-3156.2001.00793.x/full. Internet accessed Jan20th, 2012.

[32]World Health Organisation (2004). The World Medicines Situation, p. 97; available on http://www.searo.who.int/LinkFiles/Reports_World_Medicines_Situation.pdf.Internet accessed on November 27th,2011.

d. Carry the correct information and identification of the product.[33]

Inspection of distribution channels should therefore be given equal emphasis, particularly in countries where the drug distribution system has several intermediate levels and the climate unfavorable.

2.3.1. National Procurement and Official Distribution Chains of Pharmaceutical Products in ECOWAS Region

In a resource limited setting like Sub-Saharan Africa, procurement agencies or medicines regulatory authorities usually do not have a full-fledged quality assurance system. Officials from national accredited distribution chains (CAMEG, PSP, Procurement board, according to each country) in the survey countries (table below) claimed that they only distribute medicines to registered drug stores, pharmacies and hospitals.

Table 1: Central purchasing depots (accredited distribution chains)

Countries	Distributors
Benin	CAMEG[a],
Burkina Faso	CAMEG[a], Sonapharm, Cophadix, Laborex
Cote d'Ivoire	PSP[b]
Ghana	Procurement Unit of Ministry of Health
Nigeria	Nigeria
Togo	CAMEG[a]

a: Central d´Achat des médicaments Essentiels Génériques et consommables médicaux.

b: Pharmacie de la Santé Publique.

[33] WHO Expert committee on specification of pharmaceutical preparations ; available from http://whqlibdoc.who.int/trs/who_trs_902.pdf.Internet accessed on October24th, 2011

In reality you may find the same medicines distributed by CAMEG, PSP or the national procurement Unit on city market stalls, carried by itinerant hawkers along the roads or in groceries. Information obtained from workers in local pharmaceutical industries indicate that bundled packets of essential medicines are sold directly to some merchants from markets because their request is higher than that of official pharmacies and hospitals since they sell lower prices compared to pharmacies. Although a number of studies have described informal outlets such as shops and kiosks, in regard to their impact on quality assurance, more work is needed in this area, since only a few studies incorporate the full range of providers from hospitals to informal kiosk, and thus allow an analysis of the substitutability between these different provider types. At present there is no information available on the ECOWAS harmonized regulation on quality of drugs marketed in West Africa. This study is aimed to evaluate some quality parameters of the most commonly used essential drugs. The results will be useful to the ongoing harmonization process and especially to the West African Health Organization (WAHO) in developing appropriate intervention strategies to ensure that only effective drugs are allowed on the ECOWAS market and to promote the public confidence in the quality of the medicinal drugs. This will contribute towards the implementation of the Essential Drugs Concept as envisaged in the WHO Prequalification program.

2.3.2. Globalization and its Impact on liberalized Medicine Trade

With increasing globalization, the linkages between health and trade are becoming more complex and affect the performance of pharmaceutical marketing systems. The main concern is the need for better and cheaper drugs for health problems in developing countries.

The liberalization of the pharmaceutical sector has the potential to rapidly spread poor quality medicines worldwide. The proliferation of substandards in surveyed countries has a wider regional even pan African relevance in regard to patient safety, since the globalization and parallel trade of pharmaceuticals means that all medicinal products can now travel across borders with greater speed and fewer restrictions, leading to the possibility of such medicines ending up in the hands of patients**.** The health workforce is of strategic importance to the performance of national health systems as well as of disease control initiatives. The brain drain from developing to industrialized countries is a long-standing phenomenon in the health professions but has in recent years taken extreme proportions, particularly in Africa. In reality, this mobility is very asymmetrical, to the detriment of less developed countries, which lose not only much-needed human resources, but also considerable investments in education and fiscal income. For the Sub-

Saharan Africa to achieve sustainable progress towards affordable access to drugs it requires coherent policies and practices which will assist in overcoming a number of supply- and demand-driven constraints; it requires also policy options which suggest how regional cooperation could assist in providing affordable access to medicines.

CHAPTER III: Regulatory Factors

3.1. Regulatory Framework in Survey Countries.

The primary aim of drug regulation is the protection of public health. The medicines are not average 'commodities'; they are developed manufactured and marketed according to internationally recognized specifications and rules. The medicinal products should meet fundamental health needs, and access to essential medicines, according to the World Health Organization, is a fundamental human right. Thus, medicines have additional social value. Appropriate use of medicines requires a 'qualified person` to prescribe them and a trained person to dispense them appropriately before the consumer takes them. The market for pharmaceuticals is therefore not a usual market in economic terms. In this context of concerns about improving access to effective and safe medicines, it is imperative to consider how drug regulation 'fits' with other national policies in relation to health and medicines supply.

The Model Quality Assurance System (MQAS) was designed by WHO to help its agencies (UNICEF, UNAIDS) achieve the goal of a quality procurement system. The model is intended to guide them in developing their own quality assurance system. It focuses on four key activities: prequalification of pharmaceutical plants, purchase, storage and distribution of pharmaceuticals.

3.1.1. Prequalification of Pharmaceutical Products and Manufacturers.

At present, the World Health Organization (WHO) prequalification program is used as a tool to enhance the quality standard of medicines circulating in developing countries. This approach presents a double advantage firstly, prequalified companies or prequalified medicines quality control laboratories are refereed by international donators for medicines purchasing for emergency or humanitarian assistance to people in need. It has a positive economic impact on selected prequalified companies and concerned countries. Secondly the prequalification program boosts competition among local pharmaceutical companies. Nigeria and Ghana are already moving towards embracing the WHO prequalification program; Evans Medicals Plc and Swiss

Pharma NIGERIA Ltd which are local manufacturers in Nigeria have already submitted an expression of intent to the WHO regarding the prequalification program.

A WHO prequalified quality laboratory (the Mission for Essential Drugs and Supplies) established in Kenya is found to help reduce the incidences of quality failures in domestic and import supply immensely. It appears that when suppliers are aware that the quality of their products is being subject to continuous monitoring, they make sure that they export drugs that are of good quality. Fig.10

The essential medicines list, first assembled by a World Health Organization (WHO) expert panel in 1977 and revised every two years to reflect current health challenges, is an inventory of medicines that treat pressing local/regional health concerns. Medicines are identified through an evidence-based process and quality, safety, efficacy and cost-effectiveness are key selection criteria. In close cooperation with national regulatory agencies and partner organizations, the Prequalification Program aims to make quality priority medicines available for the benefit of those in need. This is achieved through its evaluation and inspection activities, and by building national capacity for sustainable manufacturing and monitoring of quality medicine[34].

3.1.2. Purchase

Poor-quality medicines particularly affect lower-income countries, where inadequate infrastructure, non-regulated drug outlets, and black market operations make drug quality surveys difficult. The Home Management of Malaria (HMM) strategy has been promoted for the timely and appropriate management of malaria in Sub-Saharan Africa[35]. Drug Information and regulation enforcement are scant. The major strategy under HMM is to train householders to better recognize and treat malaria. Unfortunately the drug sellers often lack basic knowledge and

[34] Essential Medicines List. Available from http:mednet3.who.int/prequal/default.htm. Internet accessed on April 11th,2010.

[35]World Health Organisation (WHO), 2004. Scaling Up Home-Based Management of Malaria: From Research to Implementation. Geneva: WHO; available from http://www.malariajournal.com/content/6//134; Internet accessed on September 23rd, 2011.

are influenced by advertising and profit motives[36]. Most Patients without physians´prescription buy drugs for themselves, they are more likely to be adults; more often a child or an adolescent is sent to purchase for another person. The most common Patent Medicine Vendors(PMV) in Nigeria or Licensed Chemical Shops (LCS) in Ghana behaviours are: selling the requested medicine (69%), giving their own suggestions to the customer (30%), asking questions about the illness (19%) and providing instructions on how to take the medicine (21%).Apparently PMV and LCS are perceived primarily as salespersons (69%). They only fulfilled their duties as a health care provider upon request by the patients.Self-medication for presumed bacterial or malarial infections with drugs purchased from unofficial drug vendors is a common practice in Africa. The essential drugs concept is a strategic policy that enables developing countries to improve the availability and access to drugs by the general public. The most important component of this concept is the recognition of the fact that only a few drugs are necessary for the treatment, diagnosis and prophylaxis of diseases facing the majority of people in a community. By concentrating on few essential drugs the meager insufficient resources available in developing countries could be well managed and wastage minimized. This policy encouraged the compiling of a list of essential drugs tailored to all countries health needs. It was recommended that as far as possible the drugs included in the list should be generic drugs (drugs which are off patent) as these are usually cheaper (about 30%) and have a proven safety record. Furthermore, the essential drugs concept emphasized the importance of encouraging the rational use of drugs as a means of minimizing wastages due to the misuse or excessive use of drugs. The main pillars of the essential drugs concept are: established safety and efficacy, proven quality, constant availability, affordability and rational use. Unfortunately The WHO Essential Drug Program has failed in most countries[37] because of personal financial interests at local, national and foreign levels or black market-activities.

[36]Tavrow P, Shabahang J, MaKama S, 2001. Changing harmful treatment practices among private drug sellers in rural Kenya: results of a vendor-to-vendor intervention. Book of Abstracts. The 129th Annual Meeting of the American Public Health Association. Atlanta, GA; available from www.equityhealthj.com/content/9/1/22. Internet accessed on July 24th,, 2010.

[37]Kayumba PC, Risha PG, Shewiyo D, et al. The quality of essential antimicrobial and antimalarial drugs marketed in Rwanda and Tanzania; available from http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2710.2004.Internet accessed on October 30th, 2010.

3.1.3. Storage

The assurance of the stability of pharmaceuticals marketed in developing countries (most of which have tropical climates) is a challenging issue. Poor storage conditions, high temperature and high humidity conditions generally enhance chemical degradation and may alter the biopharmaceutical properties of the drugs,[38] as it has been shown for antibiotics such as Tetracycline.[39] There are studies that have shown that high storage temperatures do not adversely affect the content of many antibiotics including Penicillins and Tetracyclines.[40] Moreover, interactions may occur when products are exposed (Appendixes 4, 8, 9) at high temperature and humidity, consequently reducing the dissolution rate.[41] Although many substandard antimicrobials may contain the appropriate amount of active ingredient, they can have suboptimal activity as a result of reduced bioavailability. Examples include Tetracyclines,[42] Co-trimoxazole,[43]Pyrimethamine.[44]The influence of storage at tropical conditions on the stability and quality of essential drugs has been one of the concerns of the WHO. Nazerali and Hogerzeil

[38]Ballereau F, Prazuck T, Schrive I, et al. Stability of essential drugs in the field: results of a study conducted over a two-year period in Burkina Faso. Am J Trop Med Hyg 1997; 57:31-6; available from http://www.ncbi.nlm.nih.gov/pubmed/9242314. Internet accessed on November23rd, 2010.

[39]Okeke IN, Lamikanra A. Quality and bioavailability of tetracycline capsules in a Nigerian semi-urban community. IntJ Antimicrob Agents 1995; 5:250; available from http://www.ncbi.nlm.nih.gov/pubmed/18611675.Internet accessed on December 12th, 2010.

[40]Hogerzeil H.V., Battersby A., Srdanovic V., Hansen L.V., Boye O., Lindgren, B., Everitt G., Stjernstrom N.E. (1991b). WHO / UNICEF study on the stability of drugs during international transport. WHO/DAP/91.1; available from apps.who.int/medicinedocs/.../s18670en.pdf. Internet accessed on Feruary 24th, 2011.

[41]Saville DJ. Influence of storage on in vitro release of ibuprofen from sugar coated tablets. Abstract Int J Pharm 2001; 224: 39–49: available from: http://www.sciencedirect.com/science/article/pii/S0378517301007347.Internet accessed on August14th, 2010.

[42]Okeke IN, Lamikanra A. Quality and bioavailability of tetracycline capsules in a Nigerian semi-urban community. Int J Antimicrob Agents 1995; 5: 250; available from http://www.ncbi.nlm.nih.gov/pubmed/18611675.Internet accessed on December 12th, 2010.

[43]Kayumba PC, Risha PG, Shewiyo D et al. The quality of essential antimicrobial and antimalarial drugs marketed in Rwanda and Tanzania: influence of tropical storage conditions on in vitro dissolution. Abstract. J Clin Pharm Ther 2004; 29: 331–8; available from www.ncbi.nlm.nih.gov/pubmed/15271100. Internet accessed on July29th,2009.

[44]Amin AA, Snow RW, Kokwaro GO.The quality of sulphadoxine– pyrimethamine and amodiaquine products in the Kenyan retail sector. J Clin Pharm Ther 2005; 30: 559–65; available from http://www.ncbi.nlm.nih.gov/pubmed/16336288. Internet accessed on July 29th,2009.

(1998)[45] conducted a study in Zimbabwe to investigate the influence of storage in a tropical climate on the quality of 13 essential drugs. Samples of the same batch of a drug were taken from the government medical stores, district hospitals and from health centers. As all studies focused on essential drugs suspected of being unstable; the reviewers conclude that, even under the most adverse tropical conditions, clinically relevant instability of essential drugs is rare[46]. This may suggest that the most likely cause of low quality is to be found during manufacturing. The practical implication of this conclusion is that careful selection of suppliers and quality control at the entry point of the distribution chain are essential to ensure drug quality.

Medicine sellers often exhibit a lack of concern about expiration dates and storage conditions, especially poor settings and the absence of national control may increase the spread of substandard antimicrobials. The challenge for public health providers is to identify and discard the poor-quality medicines available on the market. Studies have looked at the expiry status of anti-infectives at various points in the distribution chain. For example, Amin *et al*[47] audited antimalarial products in 880 retail outlets across four districts in Kenya. They calculated the remaining shelf life for 2,167 unexpired antimalarial products audited during the survey. The authors report that there was sufficient remaining shelf life for most antimalarial drugs with a median of 46 months for Amodiaquine®, 30 months for Sulfadoxin - Pyrimethamine (SP), 22 months for Chloroquine® (CQ), 17 months for quinine and 12 months for products containing Artemisinin. Overall, approximately 90% of products were within their labeled shelf life. In this study, the basic storage conditions for Antimalarials in the audited retail outlets was also evaluated using a simple set of indicators: stored off floor, out of direct sunlight, in a dry area and away from direct sunlight. Over 97% of the products audited satisfied these conditions.

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[45]Nazerali, H., Hogerzeil, H.V. (1998). The quality and stability of essential drugs in rural Zimbabwe: controlled longitudinal study. Br. Med. J. 317: 512-513; available from http://bmj.com/cgi/content/full/317/7157/512.Internt accessed on August 15th,2009.

[46]Stenson B, Lindgren BH, Synhakhang L, et al. The quality of drugs in private pharmacies in the Lao People's Democratic Republic.Int J Risk Saf Med 1998; 11:243-9; available from usaid.gov/pdf_docs/PNADH154.pdf. Internet accessed on November 26th, 2009.

[47]Amin A A, Snow R W, Kokwaro GO. The quality of sulfadoxine-pyrimethamine and amodiaquine in the Kenyan retail sector.Journal of Clinical Pharmacy and Therapeutics.2005; 30:559–565; available from www.ncbi.nlm.nih.gov PubMed: 16336288. Internet accessed on November 7th, 2009.

The minimum standards which should be considered when handling medicines are*:

a) Materials for manufacturing and pharmaceutical products should be handled and stored in such a manner as to prevent contamination and mix-ups.

b) Storage areas should be of sufficient capacity to allow for orderly storage.

c) Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required on the label (e.g. temperature, relative humidity), these should be provided, checked, monitored and recorded.

d) Materials and pharmaceutical products should be stored off the floor and suitably spaced to permit cleaning and inspection. Pallets should be kept in a good state of cleanliness.

e) Storage areas should be clean, and free from accumulated waste and vermin. A written sanitation programme such as SOP (Standard Operating Procedure) should be available indicating the frequency of cleaning and the methods to be used to clean the premises and storage areas. There should also be a written programme for pest control. The pest-control agents used should be safe, and there should be no risk of contamination with the materials and pharmaceutical products.

f) Precautions must be taken to prevent unauthorized persons from entering storage areas

g) Materials and pharmaceutical products should be stored in conditions which assure that

their quality is maintained, and stock should be appropriately rotated. The “first expire/first out” (FEFO) principle should be followed.

h) Broken or damaged items should be withdrawn from usable stock and separated.

i) Storage areas should provide adequate lighting to enable all operations to be carried out accurately and safely.

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* Personal information from GMP Module at WAHO Training for Local Manufacturers and Medicines Regulatory Authorities in ECOWAS Region. Lagos October 2010

However, it is often unclear whether a poor-quality drug is the result of deliberate counterfeiting or substandard production, transport, and storage problems[48].Lack of Good Manufacturing Practices (GMP) is common in local pharmaceutical industries in most developing countries because of many hurdles such as frequent electric power cuts and shortage of water.

3.1.4. Distribution

Most developing countries still lack their own quality assurance facilities to assess the quality of pharmaceutical products they import. Major exporters among developing countries such as China, India, and Pakistan export to other low- and middle-income countries. In many developing countries an unfortunate combination of two factors exists: On one hand, the predominance of imported finished medicine products and on other hand the lack of adequate analytical services and appropriate human resources. Regulated Imports by low- and middle-income countries come mainly from industrialized countries. Parallel trade is the legal importation of a patented drug without the authorization of the patent holder. The main driver behind parallel trade is the variation in the manufacturers' drug prices across markets. Importing occurs from countries with a low drug price relative to the price of the same drug in the importing country and where the price difference is sufficient to cover the costs of transport, registration, relabeling/repackaging, creating and inserting leaflets according to national requirements. Parallel distributors, brokers and their allies aggressively seek to avoid detection. They exploit weaknesses in border control whenever governments try to promote world commerce by reducing border controls. Pharmaceutical companies manufacture drugs and provide them to distributors or move round the pharmacies, various hospitals and other relevant institutions for onward use. The problem or the failure of pharmaceutical companies is that, instead of focusing on pharmacies, they prefer to reach the open unregulated market purposely to maximize their profit. Drugs dealers in the markets represent some manufacturers and other sole agents selling drugs; these dealers are literate, illiterate or educated but not educated in health related fields.

[48] R. Martino & M. Malet-Martino & V. Gilard& S. Balayssac Counterfeit drugs: analytical techniques for their identification Analytical and Bioanalytical Chemistry (2010) Volume: 398, Issue: 1, Pages: 77-92; available from www.ncbi.nlm.nih.gov PubMed: 20437031; Internet accessed on October 19th, 2010.

Unqualified drug sellers offer alternative drugs when the prescribed drugs are out of stock or refill prescriptions without consulting the prescriber. The majority of drug sellers or licensed chemical stores are less aware of the detrimental effects of inappropriate antibiotic use. Health authorities should endeavor to set up their own drug regulatory systems based on legislation and regulations. A study on drug sellers' knowledge in Dar es Salam-Tanzania by Massele et al. 1993 revealed that only 20% of vendors knew the correct dose of Chloroquine®. Pharmacy technicians in Thailand prescribed Rifampicin for Urethritis and Tetracycline for young children[49]. Indeed, the proliferation of substandards in surveyed countries has a wider regional even pan African relevance in regard to patient safety, since the globalization and parallel trade of pharmaceuticals mean that medicinal products can cross borders with greater speed and fewer restrictions, leading to the possibility of such medicines ending up in the hands of patients.

The liberalization of the pharmaceutical sector has the potential to rapidly spread poor quality medicines worldwide. In common practice, more than half of all disease episodes in Sub-Saharan Africa (SSA) are initially treated with home management (self-medication) by private providers, mainly through the purchase of drugs from shops and drug peddlers, before consulting an official health care center. This practice leads to misuse of medicines such as overdosing. Drug shops generally stock a range of medicines for minor ailments, basic first aid supplies and toiletries. They have been tolerated by national health authorities in many developing countries to provide a suitable entry point for government intervention to improve retail sector treatment, as they form an established network in both urban and rural areas, and their staff generally have some medical training or experience (Goodman et al. 2004)[50]. Studies in six Latino American countries indicate that in countries with little regulation, substantial misuse of antibiotics exists[51].

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[49]Thamlikitkul V. Antibiotic dispensing by drug store personnel in Bangkok, Thailand. J Antimicrob Chemother 1988; 21:125-31.Cited by Iruka N. Okeke in "Socioeconomic and Behavioral Factors Leading to Acquired Bacterial Resistance to Antibiotics in Developing" Emerging Infectious Diseases

Vol 5.No 1 Page 19 January-February 1999. Internet accessed on October 23rd, 2010.

[50]CA Goodman, SP Kachur, S Abdulla, P Bloland, and A Mills. Regulating Tanzania's drug shops -- why do they break the rules, and does it matter? Available from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2657823/pdf/ukmss-4160.pdf.Internet accessed on December21, 2009.

[51] Sahoo et al, Antibiotic use, resistance development and environmental factors: a qualitative study among healthcare professionals in Orissa, India; available from http://www.biomedcentral.com/1471-2458/10/629.Internet accessed on July 14th 2011.

Non-governmental organizations working in developing countries also use drug tenders without applying minimum quality assurance procedures (European Commission Humanitarian Aid Department 2006)[52]. The supply of good quality essential medicines is undoubtedly one of the prerequisites for the delivery of healthcare. However, there is widespread concern that drug shops frequently flout pharmaceutical regulations and prioritize profit-making over good distribution practice, leading to poor quality care, unsafe practices and behavior that encourage the circulation of substandard and counterfeited medicines.

3.2. Ineffective Drug Regulation and related Consequences

More than a decade after the World Health Organization (WHO) has called member states to establish and /or enforce regulations that ensure good uniform standards of quality assurance for all pharmaceutical products manufactured in, imported to, exported from, or in transit through their countries, still, there are several reports on the circulation of substandard and counterfeited pharmaceutical products in the markets of Sub-Saharan Africa. A study in Nigeria (Taylor et al. 2001) found that almost half of the randomly sampled antibiotic and antiparasitic drugs did not comply with set pharmacopoeial limits[53.] The illicit marketing of medicines is still rife in developing countries. The existence of substandards, degraded medicines and counterfeits on markets can be indicative of the same or similar problems of ineffective drug regulation and related law enforcement. The use of substandard and counterfeit drugs is not only a waste of resources, but may also threaten the health and lives of those who take them. Examples include the sulfanilamide incident that led to the deaths of 107 children in the United States of America in the mid-1930s[54] and the thalidomide disaster of the 1960s which caused birth defects on

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[52] J.-M. Caudron, N. Ford, M. Henkens, C. Mace, R. Kiddle-Monroe and J. Pinel. Substandard medicines in resource-poor settings: a problem that can no longer be ignored; available from http://msf.openrepository.com/msf/bitstream/10144/37334/1/Caudron_substdmeds_TMIH2008.pdf.August 23,2010

[53]Taylor, R.B., Shakoor, O., Berhens, R.H., Everard, M., Low A., Wangboonskul, J., Reid, R.G., Kalawole (J.A 2001) “Pharmacopoeial quality of drugs supplied by Nigerian pharmacies”. Lancet 357: 1933-1936; available from http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(00)05065-0/fulltext;Internet accessed on November30th,2009

[54]Geiling E, Cannon P. “Pathogenic effects of elixir of sulfanilamide (diethylene glycol) poisoning. A clinical and experimental correlation. Final report". Journal of the American Medical Association, 1938, 111:919-926;cited by. Sauwakon Ratanawijitrasin, Eshetu Wondemagegnehu. Effective drug regulation-A multicountry study. A book published by World Health Organization 2002 WHO Library Cataloguing-in-Publication Data ISBN 92 4 156206 4

children in Germany[55]. More recently, Diethyleneglycol contamination in drug preparations, such as Paracetamol, has led to multiple tragedies in Haiti and India[56,57]. In Niger, fake meningitis vaccines, administered during an epidemic in which more than 26700 people had contracted the disease, led to the deaths of 2500 peoples[58].Therefore, harmonized action is aimed at encouraging rigorous regulatory control of medicines; more action is now needed to encourage countries to establish standards which ensure that products meet the necessary, internationally accepted criteria of quality, safety and efficacy.

In Africa, illicit drug marketing is not limited to illegitimate ambulatory drug sellers or stall owners in the marketplace; it is common to find cheap and ineffective drug copies existing next to the original or generic brand in an official pharmacy, or supplied by the same wholesalers. Many dealers break the law by dispensing prescription-only drugs over the counter or providing counterfeit replacements to patients with insufficient money to purchase the original. It is therefore very important to implement measures against abusive use of pharmaceutical products.

The concerns expressed are legitimate. However, with respect to the possible adverse clinical effects of substandard drugs, the reasons why they are poor quality must be clarified. The most obvious reasons are poor manufacturing practice, inadequate quality assurance or possible decomposition of active ingredients. The latter is plausible when drugs are exposed on market stalls for weeks or even months under conditions conducive to chemical degradation of active ingredients, particularly in tropical countries (Appendixes 9, 11).

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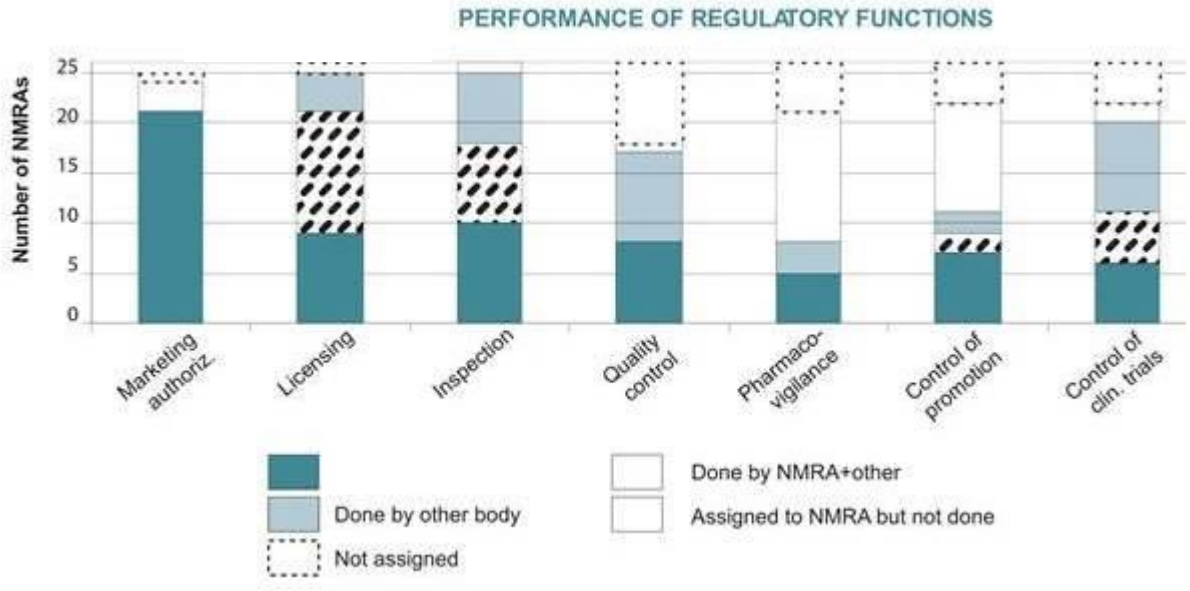
[55]Dukes G. “The effects of drug regulation: a survey based on the European studies of drug regulation”. Lancaster, MTP Press Ltd., 1985;cited by Sauwakon Ratanawijitrasin, Eshetu Wondemagegnehu. Effective drug regulation- A multicountry study. A book published by World Health Organization 2002 WHO Library Cataloguing-in-Publication Data ISBN 92 4 156206 4

[56]O’Brien KL et al. “Epidemic of pediatric deaths from acute renal failure caused by Diethylene glycol poisoning”. Journal of the American Medical Association, 1998, 279(15):1175-78.Available from www.ncbi.nlm.nih.gov/pubmed/9555756;internet accessed on January 11,2010

[57]Singh J et al. “Diethylene glycol poisoning in Gurgaon, India”, 1998.Bulletin of the World Health Organization, 2001, 79(2):88-95. Available from www.who.int/bulletin/archives/79(2)88.pdf;Internet accessed on January 11th,2010.

[58] Cockburn R, Newton PN, Agyarko EK, Akunyili D, White NJ, 2005 “The Global Threat of Counterfeit Drugs: Why Industry and Governments Must Communicate the Dangers”. PLoS Med 2(4): e100. doi:10.1371. Available from www.plosmedicine.org/.../journal.pmed.002010; Internet accessed on January 11th,2010.

The problem of substandard drugs is more pronounced in developing countries and some factors responsible for this can be identified. One is that in less resourced countries there are few functioning drug regulatory authorities. An assessment on the performance of regulatory functions conducted by the WHO in 26 African countries identified some flaws in medicines regulatory environment.[59]. In fact, most National Medicines Regulatory Authorities (NMRA) lacked sustainable funding. Another concern is that, there is a universal shortage of qualified staff and operational resources. Quality Management System that covers regulatory elements, procedures and trainings to keep staff abreast of new technology and science do not exist, also specific measures to avoid conflicts of interest are generally absent.



Source: Assessment of medicines regulatory systems in Sub-Saharan African countries Page 11 - WHO/EMP/QSM/2010.4 Accessed on October 22, 2011

The lack of systematic quality control and a non- regulated drug distribution system create an environment favorable for introducing low-quality drugs. Structures exist to inspect local

[59] J.-M. Caudron1,2, N. Ford1, M. Henkens ,"Substandard medicines in resource-poor settings: a problem that can no longer be ignored. Tropical Medicine and International Health". volume 13 no 8 pp 1062–1072 august 2008;available from apps.who.int/medicinedocs/.../s14915e;Internet accessed on January 9th,2010

medicines production sites for compliance with national requirements; but the coordination of such inspections was not well established; the insufficient of qualified inspectors (Fig. above), the lack of transport and communication means severely limited the number and quality of inspections conducted. In some of the surveyed countries the applied guidelines were not in line with Good Manufacturing Practices (GMP) and Good Distribution Practices (GDP). According to the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) about 7% of all drugs being sold around the world in 1992 were of poor quality (counterfeited or substandard). The problem is worldwide and occurs both in rich and poor countries. The impact is alarming if consideration is given to the increased treatment costs, reduced productivity, patient suffering and possible development of resistance by susceptible microorganisms.

The main concern is about their quality and efficacy with regard to their distribution, handling and storage conditions. There are three main categories of poor-quality medicines.

A counterfeit medicine is "*deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredient or with fake packaging*".[60] Counterfeit drugs do not meet quality standards and do not declare their real source for the purposes of fraud. They may be generic or innovative.

Substandard medicines (also called out-of-specification (OOS) products) "*are genuine medicines produced by legitimate manufacturers that do not meet the claimed quality specifications. For example, they may contain less (or more) active ingredient than written on the package. This may not be an intention to cheat, but may be due to problems with the manufacturing process*".[61] They are an inevitable consequence of inadequate local regulation of the pharmaceutical industry and the lack of Good Manufacturing Practices (GMP) facilities in many 'developing' countries. Poor compliance with GMP standards can lead to substandard

[60]Paul N. Newton, Sue J. Lee, Catherine Goodman, "Guidelines for Field Surveys of the Quality of Medicines: A Proposal"; available from www.plosmedicines.org.March 2009 Vol 6, Issue 3,e1000052.Internet accessed on June 9th, 2010.

[61]Paul N. Newton, Sue J. Lee, Catherine Goodman, "Guidelines for Field Surveys of the Quality of Medicines: A Proposal"; available from www.plosmedicines.org.March 2009 Vol 6, Issue 3,e1000052.Internet accessed on June 9th, 2010.

production. This may be accidental (such as human error) or the result of insufficient resources (expertise, appropriate manufacturing infrastructure, or human and financial resources). Other deliberate causes are often ignored or underestimated.

Degraded medicines "*may result from exposure of good-quality medicines to light, heat, and humidity. It can be difficult to distinguish degraded medicines from those that left the factory as substandard, but the distinction is important as the causes and remedies are different"*.[62]High temperature and humidity, and poor quality assurance during the manufacture of pharmaceutical products in less-developed countries could lead to degraded medicines.

The WHO has been tracking and documenting the incidences of substandard drugs. The records show that problems of substandard and counterfeit drugs are increasing as 50% of all reported cases occurred in the period 1993 to 1997. Most of these incidences (70%) were reported in developing countries. The report identifies the causes of the poor quality of drugs: in about 50% of all cases the formulations did not contain any drug (active substance), 20% contained the wrong active ingredient and 10% the wrong amount of the active ingredient. Only in 5% of the reported incidences did the drugs contain the right active ingredient in the correct amounts, but were judged substandard by failing other quality tests. Antibiotics represented the class of drugs with the largest number of incidences (60%) of counterfeiting (WHO, 2000), posing an even greater health risk as substandard anti-infective drugs may lead to selection of resistant strains of microorganisms, reducing the achievements made so far in combating infectious diseases. Substandard drugs are not found only in developing countries, in developed countries where the drug regulations are strictly enforced; some incidences of substandard drugs on the market have been reported. However, there is a higher prevalence of substandard drugs in developing countries as less stringent quality control measures are in place in these countries. In Kenya, the quality of metronidazole products available on the market was evaluated; all products conformed to the United States Pharmacopoeia (USP) specifications. However two formulations failed the dissolution test as they released only 46.8% and 45.8% of drug in 40 minutes (Kibwage et al.,

[62]Paul N. Newton, Sue J. Lee, Catherine Goodman, "Guidelines for Field Surveys of the Quality of Medicines: A Proposal"; available from www.plosmedicines.org.March 2009 Vol 6, Issue 3,e1000052;Internet accessed on June 9th, 2010.

1991)[63] whereas a minimum of 80% drug release within 40 minutes is required. Kibwage et al. (1992) reported that about 45% of the drugs sampled on the Kenyan market and analysed at Daru (Drug analysis research Unit) quality control laboratory on a routine basis, were of substandard quality in terms of the drug content[64.] In 1994, Roy reported on the existence of substandard formulations (37 out of 137) in Bangladesh, some of which had been found to be of acceptable quality by the local Drug Regulatory Authorities[65]. Shakoor et al. (1997) evaluated the quality of pharmaceuticals on market in Thailand and Nigeria[66]; the sampled drugs were Antimalaria and antibiotic formulations that are the most frequently used in these countries. The studies revealed that 36% of the samples from Nigeria and 40% from Thailand did not comply with the British Pharmacopoeia standards. The content of the active ingredient in some of the samples was marginally outside the official limits. Three of the substandard samples from Nigeria (2 Chloroquine and 1 Amoxicillin) and 3 from Thailand (all Chloroquine) were fakes. Since the authors could not detect impurities or degradation products (except from an Ampicillin/Cloxacillin suspension), they suggested that the major reason for substandard drugs in the developing countries was poor manufacturing practices on the part of the suppliers. Gomez et al. (1998) reported on the differences in assay results of Antimalaria drugs analyzed by the quality control laboratory of the Institute of Drug Control in Vietnam[67]; some of the drugs that had passed the quality tests in the quality control laboratory, failed when independently assessed by a World Health Organization accredited laboratory.The finished pharmaceutical products manufactured under the specified conditions as per the GMP should be able to meet

[63]Kibwage, I.O., Thuranira, J., Migosi, D. (1991). Quality of metronidazole tablet products on the Kenyan market. East Afr. Med. J. 68: 365-371,Abstract; available from www.ncbi.nlm.nih.gov/pubmed/1935731.Internet accessed on March 23rd 2010.

[64]Kibwage, I.O., Ogeto, J.O., Maitai, C.K., Rutere, G., Thuranira, J., Ochieng, A. (1992).The quality work in Daru: observations during 1983 – 1986. East Afr. Med. J. 69:577-580; available from www.ncbi.nlm.nih.gov/pubmed/1473513. Internet accessed on March23rd, 2010.

[65] Roy, J. (1994). The menace of substandard drugs. World Health Forum 8: 202-206; available from www.thelancet.com/.../PIIS0140-6736(05)7047. Internet accessed on July 11th,2010,

[66]Shakoor, O., Taylor, R.B., Berhens, R.H. (1997). Assessment of the incidence of substandard drugs in developing countries.Trop. Med. Int. Health 2: 839- 845; available from http://onlinelibrary.wiley.com/doi/10.1046/j.1365-3156.1997.d01-403.x/pdf.Internet accessed on November 24th, 2010.

[67] M., Wayling, S., Pang, L. (1998). Interventions to improve the use of antimalarials in South East Asia: an overview. WHO Bulletin Volume: 76 Suppl 1, Publisher: World Health Organization, Pages: 9-19 PubMed: 9763718; available from www.pubmedcentral.nih.gov;Internet accessed in October 12th, 2011.

the specification as defined in internationally accepted monographs. It is estimated that only 30% of the developing countries have an established and functioning drug regulatory authority (WHO, 2000)[68]. Nevertheless, most of the regulatory authorities have not established quality control laboratories. Even when these are available, they lack proper equipment and human resources to perform the work properly and/or to monitor the quality of the drugs on market. In some cases they have not instituted Good Laboratory Practices (GLP), which is required for the reliability of the analytical results. Taylor et al. (2001) evaluated the quality of 581 formulations of 27 different drugs from 35 urban pharmacies in Nigeria; the potency of 48% of the samples did not comply with the USP or BP pharmacopoeia specifications for drug content. Most of the failed samples had a drug content that was marginally below the pharmacopoeia limits.

3.3. Obsolete Drugs in Developed Countries and the Prevalence of Substandards

The standard of living contributes to the prevalence of substandard drugs in developing countries. In more than 36 developing countries, including many ECOWAS member countries, the average annual per capita expenditure on drugs by the population is less than one US dollar. This low per-capita consumption is an indicator for the inability of the people to afford basic drugs from regulated outlets. Drugs necessary for the treatment of certain tropical diseases have begun to disappear from the market because they are commercially unprofitable. Many of these drugs were discovered in the 1950s and1960s or earlier and are rarely used in wealthy countries. An example is seen in the effort to treat epidemic bacterial meningitis, caused by Neisseria Meningitides (refers to Meningococcus, a bacterium that can cause Meningitis), which is rampant in Sub-Saharan Africa. The efficacy of treatment with Chloramphenicol in oily suspension (1 intramuscular injection repeated after 48 hours) for bacterial meningitis is comparable with the traditional treatment with Ampicillin (intravenous injections 4 times daily for 10 days). The lower cost of Chloramphenicol in oily suspension which represents one tenth of the cost of the Ampicillin treatment in addition to its simple administration makes it particularly suitable to the precarious conditions in developing countries. In Nigeria in 1996, for example, more than 100 000 cases of Neisseria Meningitidis infections were reported. However, production and availability of

[68] The WHO Medicines Strategy Framework for Action in Essential Drugs and Medicines 2000-2003, WHO, Geneva : available from on http://apps.who.int/medicinedocs/pdf/whozip16e/whozip16e.pdf; Internet accessed in June 6th, 2010.

Chloramphenicol in oily suspension are no longer guaranteed because it is no longer a first-line agent for any infection in developed nations. Oily Chloramphenicol is recommended by the World Health Organization (WHO) as the first-line treatment of Meningitis in low-income countries, and appears on the WHO essential drugs list. It was first used to treat Meningitis in 1975 and numerous studies since have demonstrated its efficacy. It is the cheapest treatment available for meningitis (US$5 per treatment course, compared to US$30 for Ampicillin). Non-professional importers and less equipped local manufacturers use such opportunities to substitute the unmet needs with poor quality or substandard versions of Chloramphenicol. In developing countries, drugs are known to consume more than 40 to 60% of the total public and private spending on health, while in the developed countries it is limited to about 15 to 20% (WHO, 2000). Among the major reasons for these differences is the increased frequency of contracting diseases in the developing. Pharmaceutical retailers in Sub-Saharan Africa include a very limited number of formal pharmacies, and numerous general stores that sell a range of groceries and household products. Medicines are also sold by small drug shops in many ECOWAS (Economic Community of West Africa States) areas. What is amazing is that some of these illicit drug stores are closed by city council officials not for non-conformity to the medicines storage standards or regulatory requirements but for not paying taxes. This means that the national authorities recognize the existence of such illegal and non-regulated outlets but turn eyes closed. However, the question how medicinal products reach illegal vendors remains without answer. In the center of market places and bus stations, you come across many illegal drug store handlers. One of the most rational options was to adopt the World Health Organization's (WHO) essential drugs concept.

A number of recent initiatives have been established to address the problem; most notably the importance of encouraging the rational use of drugs as a means of minimizing wastages due to the misuse or excessive use of drugs. Regular surveillance of the quality and bioequivalence of pharmaceuticals on the market in Finland has identified amongst different brands of erythromycin tablets, one with a very low bioavailability (Venho et al., 1987). This brand had to be withdrawn from the market. However, there is more prevalence of substandard drugs in the developing countries in general as less stringent quality control measures are in place in these countries. The peddlers or itinerant hawkers procure the medicines in blister without package leaflet from merchants in markets and sell them from house to house or in rural areas. The peddlers are the only distributors who accept credits, this means medicines are sold on the local market day and if the consumer has no money, he may reimburse the next market day (periodically one or two market day per week). Other procurement facilities are Caritas and religious associations which

have easy access to procure medicines from pharmaceutical factories with the aim to redistribute them through hospitals with health care professional staff. There, free distributed medicines are stolen by scrupulous staff and allied patients who resell them to merchants in markets at reduced price. Usually, the seller and the customer discuss only about the price and expiration date; other quality aspects are not relevant in such transactions.

3.4. Chaotic Drug Distribution Network

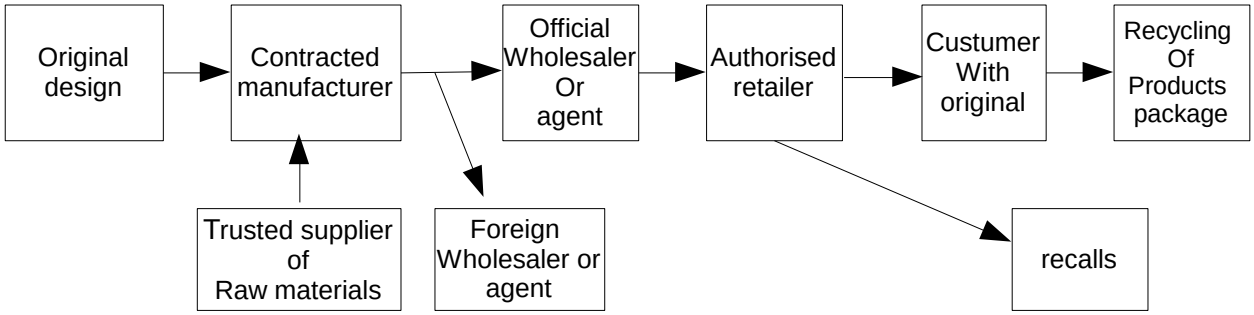
Drug distribution network in surveyed countries consists of chaotic open markets which act as major sources for procurement, medicine stores, pharmacy outlets, private and public hospitals, wholesalers/retailers and local pharmaceutical manufacturers, agents or representatives of foreign suppliers. The result of this chaotic drug distribution makes drug monitoring very difficult. In addition, it gives room to drug hawking in buses, kiosks, by illiterate vendors whose aims are solely profit oriented. The medicines are left under conditions that may facilitate the deterioration of the active ingredients (Erhun, 2001)[69]. Medicines are sold just like any other goods of the trade (Appendixes.1, 11). Poor drug regulation which affected the pharmaceutical sector over years, helped the raising of drug markets which are not registered premises and are well established all over the region. Most of the drug wholesalers and importers supply drugs to these open drug markets because they make more profit from there. Consumers purchase such products with a hope of obtaining the genuine one, and most of the time these drugs are distributed through unauthorized channels[70].There is always demand for cheap drugs due to easier access, better affordability and sometimes better availability as compared to public health facilities. Hence illegal traders will quickly fill the gap in supplies.

[69]Erhun W.O, Erhun M.O, Babalola O.O (2001) Drug Regulation and control in Nigeria: The challenge of counterfeit drugs. Journal of health and population in developing countries, 4 (2): 23-34.NAFDAC NIRERIA May 2002; available from www.nigeriapharm.com/.../Drug_regulation.pdf;Internet accessed on April 21st, 2010.

[70]Erhun W.O, Erhun M.O, Babalola O.O (2001) Drug Regulation and control in Nigeria: The challenge of counterfeit drugs. Journal of health and population in developing countries, 4 (2): 23–34. NAFDAC Nigeria. 2002–05; available from www.nigeriapharm.com/.../Drug_regulation.pdf.Internet accessed on April 21st,2010.

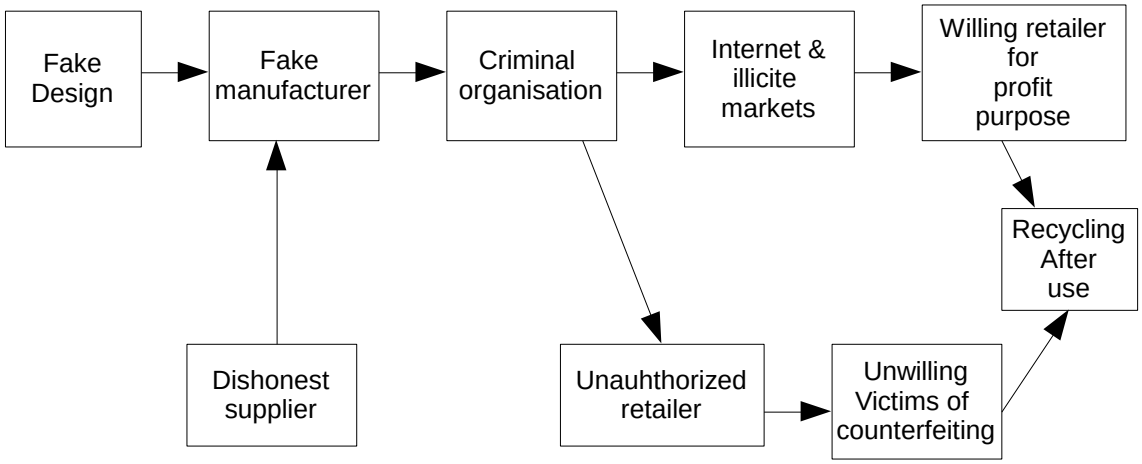
According to Brains (2004: Figures 2a, 2b) drug distribution chains in resource limited countries consist of different actors within the legitimate supply chain and the illegitimate supply chain. The legitimate supply chain consists of original products from the designers down to consumers; and is regulated and monitored at all levels. The products are then bought by wholesalers for distribution, from there the authorized retailers buy and dispense to the consumers. Moreover, if the product does not match its predetermined specifications it will be removed (´´recalled´´) from the market. The illegal supply chain is made up of dubious distributors and their allies who can copy other products and present them as original. The product design is faked with the aid of fake manufacturer in criminal organization who distributes the drugs on local markets and via internets. The products go to an unauthorized retailer who buys it for profit purposes even when he knows the source is suspicious, dispenses the fake product to an innocent victim.

Figure 2a: Legitime Supply chain



Source: Brain (2004)

Figure 2 b: illegal supply chain



Source: Brains (2004) welcome to the anti counterfeit brains. Available at www.acbrains.com/supplychain_eng/supplychain_eng.html

Source: Brains(2004) welcome to the anticounterfeit brains. Available at www.acbrains.com/supplychain_eng/supplychain_eng.html;accessed on July 13th, 2010

CHAPTER IV: Factors influencing the Pharmaceutical Marketing

4.1. Factors influencing the Proliferation of Substandards and Counterfeits

4.1.1. Medicines Price

The high cost of pharmaceutical products limits access to treatment. Drug prices should vary according to some measure of national wealth and affordability. *The agreement at World Trade Organisation (WTO) ministerial conference in Doha to minimise the adverse effects of patent protection on public health has increased the relevance of differential pricing as a means of improving access to patented medicines in low income countries*[71]. Income per capita and the cost of medicines are key factors affecting demand and thus influence the choice of medicine provider, the choice of drug, the quantity and dose purchased. In less resourced countries like Sub-Saharan Africa, cost is frequently mentioned as a reason for not using health facilities (Williams and Jones 2004)[72]. There are higher chances for fake drug proliferation when medicine prices are high. Scrupulous distributors take advantage of consumers who cannot afford high priced quality drugs by supplying them with cheaper substandard or counterfeit drugs. The treatment costs are generally cheaper at drug shops because there are no consultations or laboratory fees and small quantities like a single blister or two-three tablets/capsules of drugs can be purchased (Adome, Whyte and Hardon 1996)[73]. The majority (90.2%) of Nigerians cannot afford good medicines as they live below an income level of US 2$ a day[74]. The baseline survey also showed a low availability of essential medicines in health facilities. Only 46% of

[71] The Doha Development Agenda. Issue Brief available from www.nathaninc.com; Internet accessed Jan.21st ,2012)

[72]Williams, H.A., and C. O. Jones. 2004. "A critical review of behavioral issues related to malaria control in sub-Saharan Africa: what contributions have social scientists made?" SocSci Med 59:501-23; available from http://www.ncbi.nlm.nih.gov/pubmed/15144761Internet accessed February 18th,2011

[73]Adome, R.O. S.R. Whyte, and A. Hardon. 1996. Popular Pills: Community Drug Use in Uganda.Het Spinhuis Pubisher Amsterdam. ISBN 90-5589-0553.Documentation from NAFDAC-Ikeja Lagos January 18th, 2010.

[74]HAI Africa (2008) Medicine prices in Nigeria, prices people pay for medicines. Available online at http://www.haiafrica.org/downloads/price_SDurveys/Nigeria.pdf.Internet accessed on November 13th,2011.

essential medicines were found in the health facilities[75]. Governments and local pharmaceutical industries face the dilemma of "make or buy?" Often, a politically strong domestic industry will persuade a government to purchase locally manufactured pharmaceuticals, even if it is more costly than purchasing imported drugs. These decisions have important implications for pharmaceutical industrial policy and for health care policy. In the Philippines, for example, the senate has approved a bill called affordable medicines; act that will help dumping the prices of drug so that it can be affordable and their domestic pharmaceutical companies may have a larger sale in their drug market. In addition, it will help reduce the incidence of imported fake drug into the country[76].

4.1.2. Demand Exceeding Supply and Consumer Awareness

The supply and distribution of medicines are a fundamental aspect of the success of any health system. Public supply chain in Sub-Saharan Africa is afflicted by inadequate financing and a devastating reduction in the healthcare workforce; the formal sector is generally limited to urban areas. Well-trained health personnel are scarce and cannot serve the entire population, especially in rural areas. Faith based and other non-governmental services supplying health care handle less than 15% of a country's pharmaceutical needs. Irrational use of medicines is a major problem in the region. It is estimated by WHO that more than half of all medicines are prescribed, dispensed or sold inappropriately and that half of all patients do not take them correctly. Irrational use of medicines covers instances where there is unnecessary prescription of drugs, especially antibiotics, prescription in wrong dosages, inappropriate self-medication, and under dosing or over dosing. This occurs due to a lack of awareness and knowledge among patients. This increases the financial burden on the poor, who often have to purchase the medicines out of own pocket. There is a huge gap in access to medicines in rural area. Disruptions in the supply of medicines undermine health outcomes as supply chains have an impact on the availability, cost and quality of medicines. People are encouraged to buy from unofficial distributors because

[75]HAI Africa (2008) Medicine prices in Nigeria, prices people pay for medicines. Available online at http://www.haiafrica.org/downloads/price_Surveys/Nigeria. pdf. Internet accessed on November 13th,2011.

[76] Barbara Mae Dacanay, Bureau Chief Published:"Philippine cheap medicine bill approved, April 2008".published: 17:19 April 29, 2008 ; available on www.gulfnews.com/news/world/philippines/philippine-cheap-medicine-bill-approved-1; Internet accessed on December 15th,2011.

drugs often are not available in government hospitals. Consequence, unqualified drug sellers offer alternative drugs when the prescribed drugs are out of stock or refill prescriptions without consulting the prescriber[77] The following figure shows all probable factors influencing the proliferation of unwholesome medicines in resource limited countries. The consequences of the use of such medicines may vary from therapeutic failure to the occurrence of serious adverse events and even death. Proper drug quality monitoring, enforcement of laws and legislation, an effective and efficient regulatory environment, as well as awareness and vigilance from stakeholders can help tackle this problem.

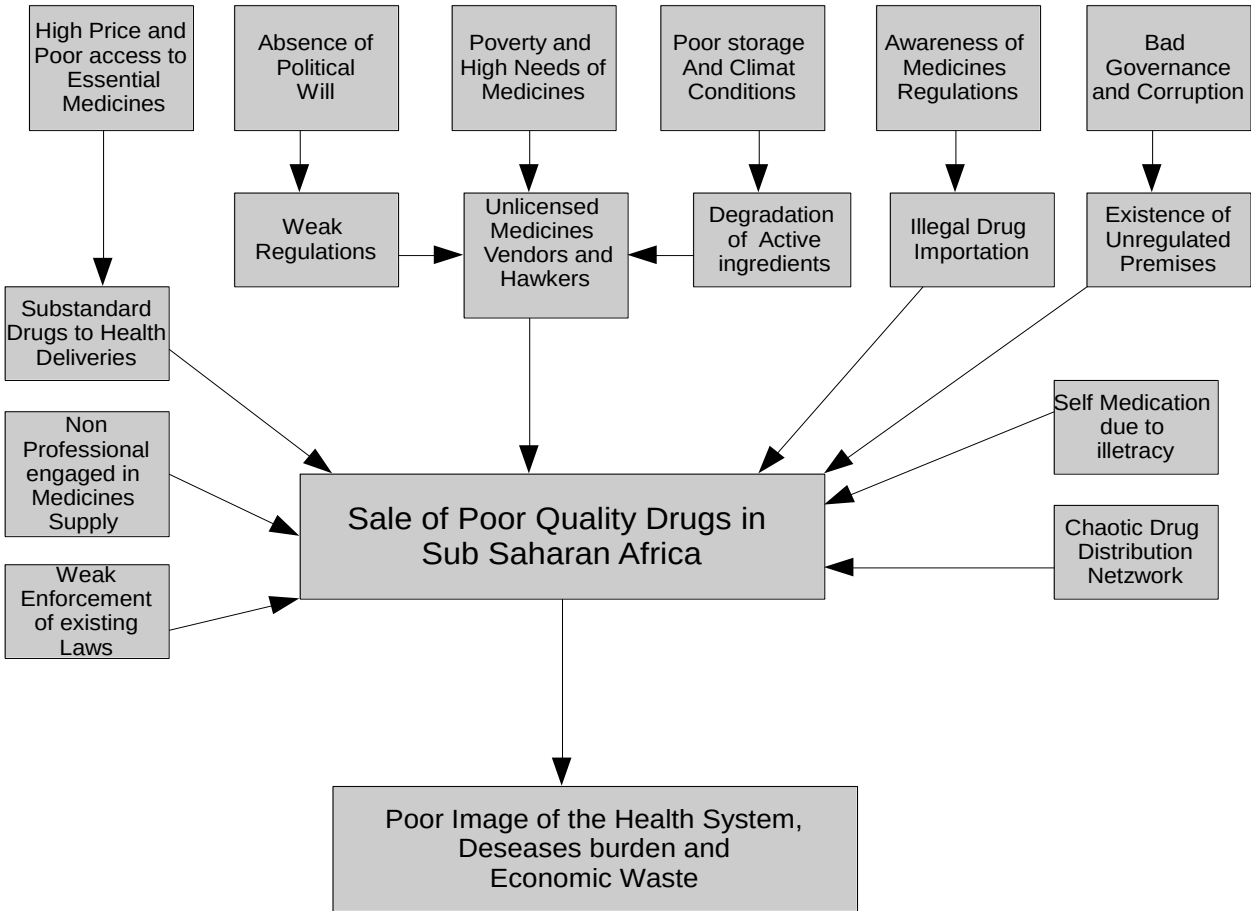


Fig 3: Factors influencing the Proliferation of unwholesome Medicines in Sub-Saharan Africa

[77] Iruka N. Okeke, Adebayo Lamikanra, and Robert Edelman. "Socioeconomic and Behavioral Factors Leading to Acquired Bacterial Resistance to Antibiotics in Developing Countries." Emerging. Infectious Diseases Vol. 5, No. 1, January. February 1999.; available from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2627681/pdf/10081668.pdf. Internet accessed on February 9th, 2011.

PART 3: METHODS AND MATERIALS

CHAPTER V: Methodology

5.1. Objectives of the Study

This study is aimed at evaluating the regulatory flaws and some quality parameters of the most commonly used essential drugs. The results will be useful to the ongoing harmonization process and especially to the West African Health Organization (WAHO) in developing appropriate intervention strategies to ensure that only effective drugs are allowed on the ECOWAS market and to promote the public confidence in the quality of the medicinal drugs. This will reinforce the implementation of the Essential Drugs Concept as envisaged in the WHO guidelines.

As a result, this will form an important supplement appeal for awareness to what has already been explored in country specific manner in the previous publications. Also this paper assess the problems caused by substandard drugs and the effectiveness of regulations designed to prevent such medicines from entering the harmonized medicine´s market in the ECOWAS region.

With aim to find out if counterfeit medicines/substandards are due to manufacturing deficiency or deliberated misleading.

5.2. Analytical Methods

Nowadays, the first step in detecting counterfeit drugs is to compare the physical appearance and text on packets, leaflet inserts, and blister packs of suspected samples with those of known genuine products. However, with increased counterfeiter sophistication, this careful visual inspection is not sufficient to distinguish between fake and authentic drugs. It must therefore be followed by chemical analysis, includes High-Performance Liquid Chromatography (HPLC), considered as the gold standard analytical method in drug analysis, but also with simple in-field assays [e.g., colorimetric test and Thin-Layer Chromatography (TLC)] or more advanced laboratory techniques [e.g., Mass Spectrometry (MS), vibrational spectroscopies (Raman or IR), and nuclear magnetic resonance (NMR) spectroscopy].

We used information gathered during research journey in some ECOWAS countries, interviews with local stakeholders. Questions concerning regulation and illegal behavior are inevitably highly sensitive and there was a risk that medicine shop staff would decline to participate or fail to provide full and truthful answers. Sensitive questions on regulation were asked towards the

end of the interviews; as a result, no drug stores refused to participate in any data collection (selling of medicines) activities. Literature from WHO home page, NAFDAC home page, Google and Pubmed were also consulted.

The major limitation to the thesis is the social and financial situation in which I had to complete the work, together with the distance from the concerned region (Sub-Saharan Africa) and my residence country (Germany) had impacted on the volume of collected information.

The analytical methods permit a qualitative and quantitative description of the chemical composition of a drug. Therefore they can be readily used to not only identify poor quality medicinal products but also to distinguish between counterfeit, substandard or degraded drugs.

In the present dissertation, visual inspection (organoleptic test), X-ray diffraction, Rama spectroscopy, and the HPLC have been used for chemical analysis of the collected samples.

Table 2: laboratory methods of analysis to investigate medicines quality and their respective advantages and disadvantages.

Separation Technique	Pros	Cons
X-ray diffraction (XRD)	Enables identification of inorganic and organic excipients, and crystal form	Extremely high cost, skilled Operator required. Not all organic Components may be detected.
Raman spectroscopy	Can identify unknown Active Ingredients and verify quality. In many cases, may work through packaging Very sensitive. Portable	Requires relatively pure sample Excipients may fluoresce, making measurements difficult Costly, but less expensive than NIR
High Pressure Liquid Chromatography (LC) (also referred to as HPLC)	One of the most widespread pharmaceutical analysis techniques. Able to identify compounds by spectrum database comparison. Offers peak purity assessment	Requires solvents, expensive columns, and trained personnel. Cost depends on detector used

5.2.1. Organoleptic Test

The first step in identifying potential substandard/counterfeit medicines is the careful visual inspection of the product, its packaging and labeling. Through a close observation of each pharmaceutical preparation, detailed organoleptic descriptions of the outer containers, the

blisters, the package inserts and the dosage forms (capsules or tablets) are checked for each sample. Moreover, other important details such as the manufacturing and expiry dates, the registration, the batch/lot number, the indications, cautions and the storage conditions are read. The following examples are visual inspection done on collected antibiotics during my research journey in some West African countries.

Tetra250®: Active Substance: Tetracycline HCL Capsules 250mg.

Manufacturer: Sprukfield (UK) SARL BP. 1218 Rue 23 Zone Portuaire, Lome (Togo).

MainOffice: First Floor. Kirkland. Peterborough Road HA1 2AX.UK. www.sprukfield.com.

Procurement place: Lome (Assigame) Togo

Procurement date: March 9th, 2010

Concerns:

No packaging leaflet attached. On the blister no instructions concerning side effect, dosage is not specified; it is written: (as directed by the physician), no indication for the user on out packaging.

Cipro 500mg USP®:

Manufacturer: ZMC Hamburg GmbH, Germany. ZMC HAMBURG GMBH GERMANY is an oversea subsidiary of Zhejiang Medicine & Health Products Export & Import Co., Ltd., http://www.sinoheal.com/

Procurement place: Assiganme Market in Togo.

Procurement date: March 9, 2010.

Concerns:

The package leaflet comprises many mistakes such as dosage form: ciprofloxacin. This should be tablet, capsule, injectable, or liquid.

Cipromax fort 500®:

Ciprofloxacin Tablets USP.

Manufacturer: Greenfield Pharmaceutical, Jiangsu (China)

Procurement place: Assiganme Market in Togo

Procurement date : March 9, 2010.

Concerns:

False translation of the instructions on the package (tenir tous les medicaments **à portée** [should be ‘**’hors de portée**’’ des enfants);

Poor legibility (type size under 7) of the package leaflet (readability).

RGI Doxycycline 100mg capsules®:

NAFDAC Reg.No.A4-2490.

Manufacturer: Richy Gold International Ltd. 103c Amuwo-Odolin Industrial Scheme Oshodi-Apapa Expressway, Lagos (Nigeria).

Procurement place: Assiganme Market.

Procurement date: March 9th, 2010.

Concerns:

It was mentioned on the package: Indication: Please refer to the leaflet although there was no leaflet in the package.

“Store in a cool, dry and dark place” was translated “Entreposer dans une place fraiche et sèche”. This is not the correct translation.

5.2.2. Mini lab Test (Visual inspection and disintegration test) Table 1

Quick release tablets and capsules must pass disintegration test; they should disintegrate in water at 37°C in less than 30minutes. It´s a major defect, if a product doesn’t pass this test*

* A concise Quality control Guide on Essential Drugs and other Medicines.Vol.1 on colour reaction tests

5.3. Use of Advanced Analytical Techniques:

5.3.1. X-ray diffraction (XRD):

Definition: XRPD (X Ray Powder Diffraction) is used to detect and quantify crystalline impurities, to determine the crystallite size of a compound analyze and optimize final dosage forms; it detects and analyzes the used fillers in capsules/tablets.

The following spectrums are the outcome of the application of X-ray diffraction at the pharmaceutical Technology of the institute of pharmacy –university of Bonn.

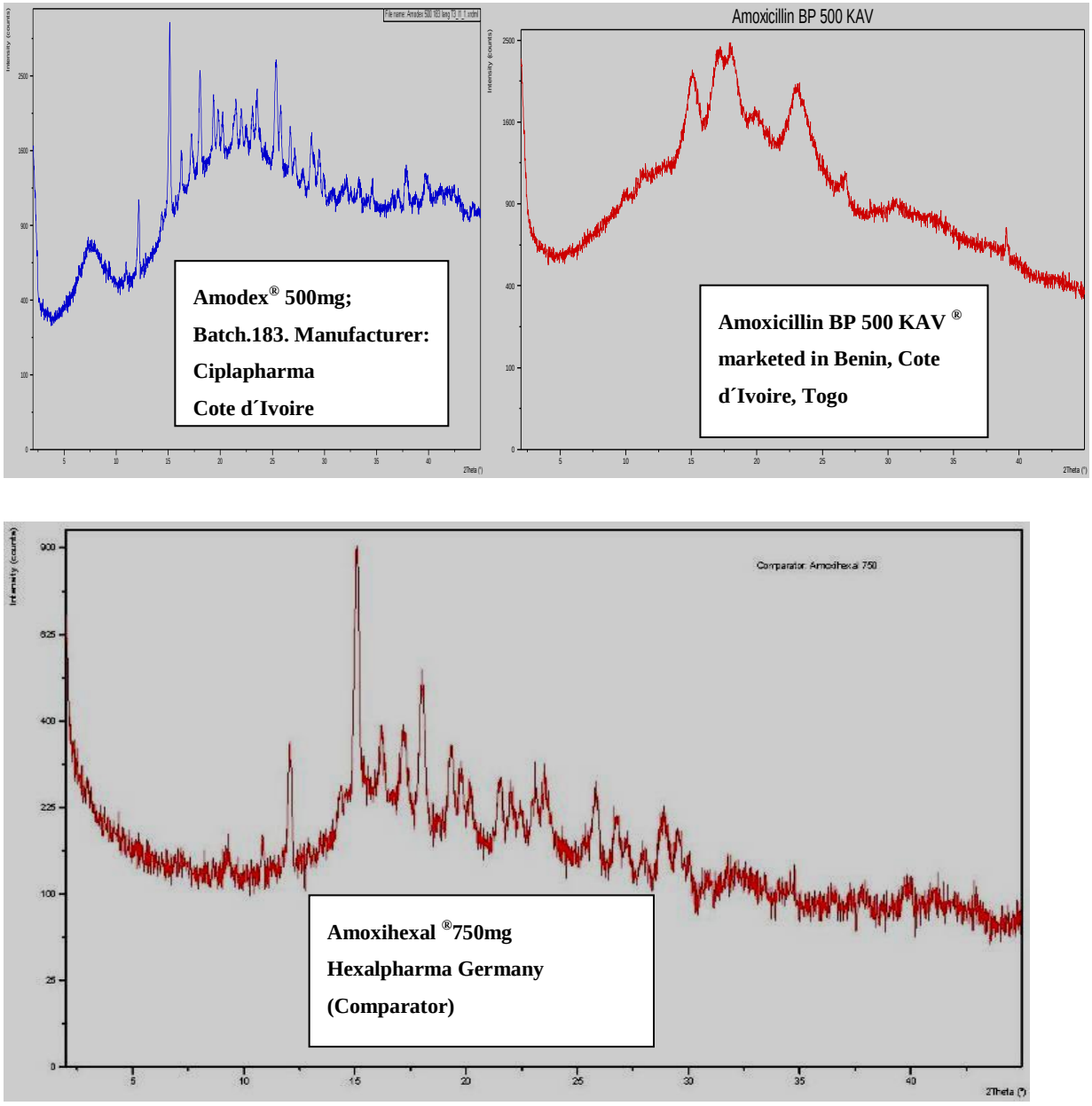


Figure 4: X-ray diffraction applied to different Amoxicillin tablets

5.3.2. Raman Spectroscopy*:

5.3.2.1. Experiment Tools

Instrument 1: TruScan Raman Analyser

Definition: The TruScan handheld Raman analyzer is an instrument for identity tests in pharmaceutical quality control and for counterfeit testing of pharmaceutical products. It is a non-destructive technique that reveals information about the chemical composition and crystallographic structure of manufactured and natural materials.

It compares the Raman spectrum of a sample with a stored spectrum of a reference sample with proven identity.

Instrument 2: (First defender RM) A handheld Raman spectrometer for forensic investigations.

It has an on-board spectral library of about 8.500 chemical substances. Most of our samples gave good Raman spectra that could be analyzed. In most cases the Active Pharmaceutical Ingredient (API) was identified in the product with comparison with available comparator.

In both methods sample testing had to be limited to samples for which reference spectra / substances were available.

Samples tested using First defender RM from Servantech (see Table 3 in section5.3.2.2)

* Introduction to Raman spectroscopy. Available from www.ahurascientific.com. Internet; accessed on June 27th, 2010

TruScan Handheld Raman Analyzer

First Defender RM Raman Analyzer (for forensic investigations)

5.3.2.2. Experimental

Raman spectroscopy is a kind of vibrational spectroscopy that uses a laser for vibrational excitation of the sample. Because it works in the visible spectrum (from the laser wavelength of 785 nm to approximately 1000 nm) it is able to measure through transparent packaging like glass or transparent plastics. For samples like tablets or capsules the Raman scattering signal comes from the surface – therefore coated tablets and capsules have to be opened to measure the active ingredients.

The measurement mode had to be chosen according to the kind and packaging of the sample:

Table.3: Measurement mode and related pharmaceutical forms

Sample	Measurement
Uncoated tablet, transparent blister	Measured directly through the blister
Uncoated tablet, non-transparent blister	Measured directly, after opening the blister
Coated tablets	Measured directly, after breaking the tablet or removing the coating
Capsules	Measuring of the capsule content in a glass vial

A typical measurement took a few seconds and mostly less than 1 minute (including spectral analysis). Only for a few samples showing strong fluorescence the measurement took longer – in some of these cases the spectrum could not be interpreted because fluorescence was much stronger than the Raman signal. Fluorescence can be a characteristic of the original product, but may also be caused by impurities, e.g. in counterfeits or degraded products.

5.3.2.3. Findings

Table 4.Results of the Raman measurements of some collected samples:

Product, Batch/ Expiration date.	Manufacturer	Appearance, Packaging	Spectrum	Identity test
ERY® 500mg Batch:659 Expires 06/2012	Sophartex 28500 Vernouillet France	White Tablet in transparent blister	Good spectrum very similar to Erythromycin spectrum)	No comparator to confirm
Erythromycin Stearate tablets BP 500mg,Batch: 227, Expires. 6/12	Strides	Red Tablets, coated	Good spectrum	Confirm with Erythromycin stearate in laboratory
Amodex® 500mg Batch: 186, Expires Nov 2012	Synthelabo	Capsule beige/ brown	Good spectrum	No Amoxicillin comparator available
Chloramphenicol 250mg, Batch165, Expires Oct.2011	Bailly-Creat	Capsule white	Good spectrum	Confirm with Chloramphenicol In laboratory
Chloramphenicol Capsules 250mg	M&G Pharm.	Capsule white	Good spectrum	Confirm with Chloramphenicol In laboratory
Piroxicam Tablets 20mg,Batch: 090601, Expires :04.06.12	SPGC Sine Pharma	Light yellow tablets	Good spectrum	Confirm with Piroxicam originator
Ciprofloxacine 500mg,Batch illegible Expires 03/2012	Strides Arcolab Bangalore India	White tablets in transparent blister	Good spectrum	No Ciprofloxacin comparator in laboratory

Product, Batch/ Expiration date.	Manufacturer	Appearance, Packaging	Spectrum	Identity test
DOXIN® Doxycycline 100mg	Yangzhou No 3 Pharmaceutical Ltd Jiangsu China	Capsules green	Fluorescence, but peaks observed with Raman	different crystal structure
Doxycycline Capsule 100mg, Batch:1350018 Expired Jan.10	LETAP Pharmaceuticals. Accra. Ghana.	Capsules green	Fluorescence	different crystal structure
Doxycycline HCl 100mg,Batch 7365, June2010	Pharmaquick Cotonou - Benin	Yellow tablets	Fluorescence	different crystal structure
Doxycap® Doxycycline 100mg, Batch: AK0256 Expires:8FEB.2010	Hovid Accra-Ghana	Capsule pink/green	Fluorescence, but Raman peaks	Doxycycline hyclate
Erythrofil® (Erythromycin stearate) 250mg.Batch S0754 Expires :May 2010	Fourrts (India) 603 103 Tamil Nadu	Pink tablets	Good spectrum	Erythromycin stearate
Ampicillin-3H2O 250mg, Batch : illegible Expires:Nov.11	LETAP Aaccra-Ghana	Capsule red/black	Good spectrum	different crystal structure from the comparator
Maloxine® (Sulphadoxine 500mg + Pyrimethamine 25mg), Batch: EM-396, Expires 03/ 2011	Shreechem Lab.	White tablets (in non-transparent packaging)	Good spectrum	Sulfacetamide (Sulphadoxine comparator not available
Metronidazole Tabl. 0.2g, Batch: 081008 Expires:2011/10/30	SINE	White tablet	Good spectrum	Confirm with Metronidazole in laboratory

5.3.3. High-Performance Liquid Chromatography (HPLC)

Chemical

The following chemicals and reagents were kindly provided by the Institute of Pharmacy and Food Chemistry in Wurzburg; as reference,

Ciprofloxacin AL 500 mg (AliudPharma),

Doxycycline Stada TABS 100mg and

Amoxicillin pure substance used for educational purpose (experiments. titration).

Acetonitrile, Triethylamine, Phosphoric acid, Potassium dihydrogenphosphate Sodium hydroxide were bought from FLUKA and were all of analytical grade, Millipore-water.

Table5. HPLC Components for Ciprofloxacin and Doxycycline

	Ciprofloxacin	Doxycycline
Column	reverse phase ODS C18 column 250 mm × 4 mm (Phenomenex MAX-RP)	reverse phase ODS C18 (2) column 250 mm × 4,6 mm, 5 µm particle size
Column temperature	ambient temperature (25°C)	ambient temperature (25°C)
Detector	UV diode array detector wavelength: 278 nm	350 nm
Injection volume	50.0 µL.	10 µL
Mobile phase	2,45 g o-phosphoric acid were dissolved in 1000,0 ml Millipore-water and adjusted to pH=3.0 with Triethylamine	Millipore water, acetonitrile and perchloricic acid were mixed (74:26:0.25) and pH was adjusted to 2.5 with 5 M NaOH
Flow rate	1.5mL min^{-1}	1.0 mL min^{-1}

We analyzed tablets, capsules, containing either ciprofloxacin, Doxycycline, Amoxicillin. In absence of Ciprofloxacin CRS (Chemical Reference Substance), Doxycycline hyclate CRS, we used: Ciprofloxacin AL 500 mg (Aliud Pharma); Doxycycline STADA TABS 100 mg.

The content of active ingredients and excipients was determined quantitatively using validated HPLC-UV methods. All analyses were done according to European pharmacopoeia requirements.

5.3.3.1. Ciprofloxacin

The liquid chromatography system used in the present study consisted of an Agilent Series 1200 liquid chromatography equipped with a quaternary pump, a column thermostat (set to 25 °C), an automatic injector, an UV-VIS detector (set wavelength: 278 nm) and a degasser. A reverse phase ODS C18 column 150 mm × 4 mm, 4.6 mm diameter (Phenomenex HydroRP) was used and maintained at ambient temperature. The used standard was: Ciprofloxacin AL 500 mg (AliudPharma).

Tested ciprofloxacin samples in the following table:

Table 6: Tested ciprofloxacin samples

	Brand Name	Active ingredient	Strength/Dosage form	Procurement site
X1	Ciprofloxacin Strides	Ciprofloxacin	500 mg / tablet	Burkina Faso
X2	Cipromax fort®	Ciprofloxacin	500 mg / tablet	Assiganme Market Togo
X3	Cipromax 500®	Ciprofloxacin	500 mg / tablet	
X4	Cipromax 500®	Ciprofloxacin	500 mg / tablet	Phyto Riker Accra Ghana
X5	Shalcip 500®	Ciprofloxacin	500 mg / tablet	Accra Ghana
X6	Ciproxamed 500®	Ciprofloxacin	500 mg / tablet	Lomé-Togo
X7	Cipromed 500®	Ciprofloxacin	500 mg / tablet	Adjame -Abidjan Cote d´ivoire
X8	Ciprobiotic forte®	Ciprofloxacin	500 mg / tablet	Assiganme Market Togo
X9	Ciprofloxacin AL	Ciprofloxacin	500 mg / tablet	Germany

The mobile phase was prepared as follows:

2.45 g o-phosphoric acid were dissolved in 1000, 0 ml Millipore-water and adjusted to pH=3.0 with Triethylamine. The elution was isocratic with 83 percent aqueous phase and 13 percent of acetonitrile. A flow rate of 1.5mL min-1 was maintained. Injection volume was set to 10 µL for the assay method and 50 µL for the impurities method.

Calibration standards were prepared as follows:

For linearity and calibration, five samples of Ciprofloxacin CRS were weighed into 100.0 ml flasks and brought to volume with mobile phase to obtain concentrations of 0.06, 0.25, 0.37, 0.50, 0.62 mg/ml). The solutions were sonicated to obtain maximum dissolution. Each sample was injected three times and average peak areas were calculated.

The calibration curve was set up plotting obtained peak areas vs. concentration of ciprofloxacin; R^2 was calculated at 0.9999 (Fig.5):

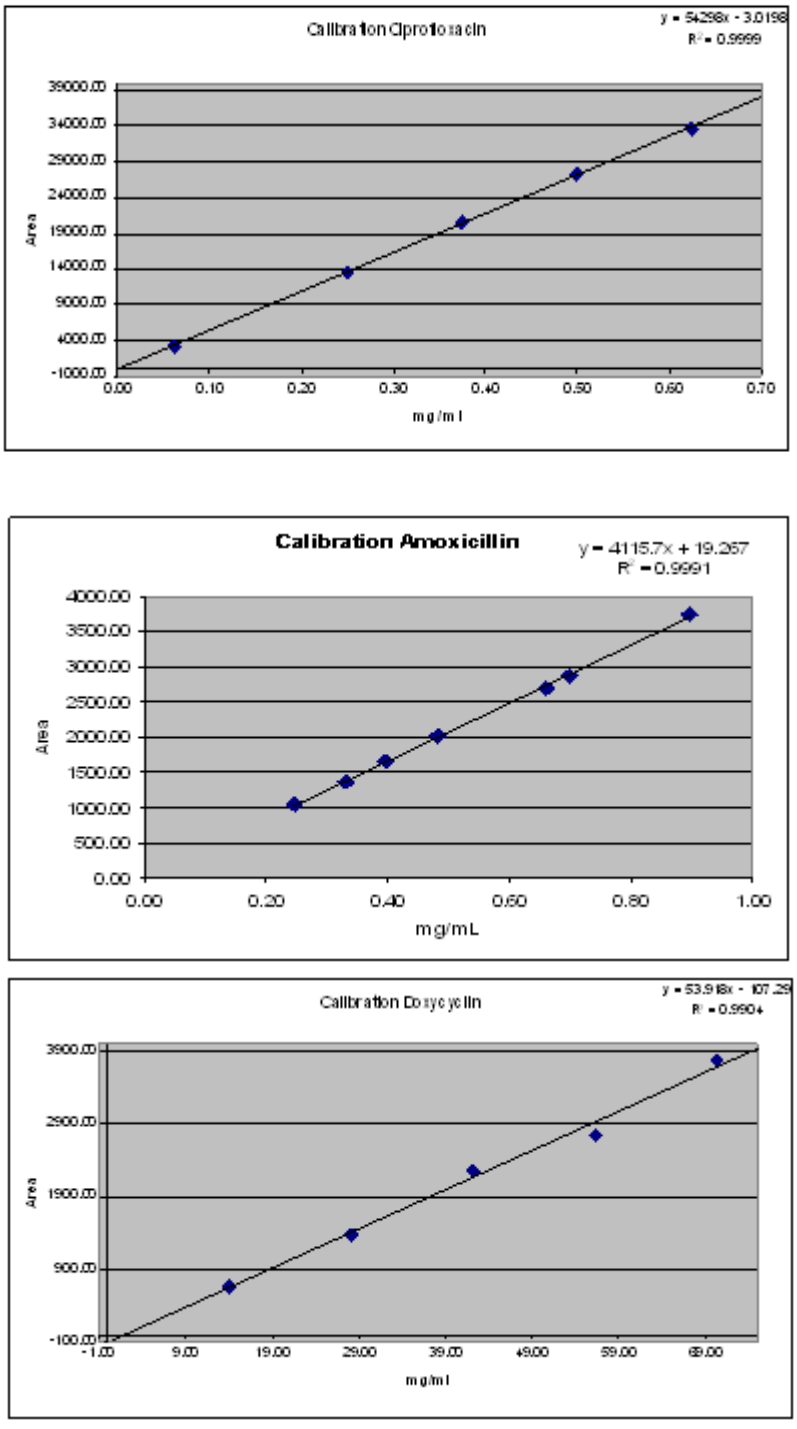


Fig.5: Calibration Curves for Ciprofloxacine, Amoxicilline Doxycycline,

Table7: Assay of ciprofloxacin, Doxycycline and Amoxicillin samples

Sample No.	Name ®	Active ingredient (declared)	% of declared content	
X1	Ciprofloxacin Strides	ciprofloxacin	**97.02**	**ciprofloxacin**
X2	Cipromax fort	ciprofloxacin	**97.72**	
X3	Cipromax 500	ciprofloxacin	**100.42**	
X4	Cipromax 500	ciprofloxacin	**97.91**	
X5	Shalcip 500	ciprofloxacin	**97.34**	
X6	Ciproxamed 500	ciprofloxacin	**95.13**	
X7	Cipromed 500	ciprofloxacin	**97.33**	
X8	Ciprobiotic forte	ciprofloxacin	**99.22**	
X9	Ciprofloxacin AL	ciprofloxacin	**98.77**	
X1	TetracyclinSprukefield	tetracyclin*	**98.32**	**doxycycline**
X2	Doxin	doxycyclin	**118.51**	
X3	Rogodox	doxycyclin	**116.88**	
X4	Doxynor	doxycyclin	**110.15**	
X5	DoxycyclinPharmaquick	doxycyclin	**98.54**	
X6	Doxycycline Capsules	doxycyclin	**162.19**	
X7	Doxycycline Capsules	doxycyclin	**112.40**	
X8	Doxycap	doxycyclin	**116.70**	
X9	Doxycycline HCl 100 mg	doxycyclin	**103.84**	
X10	Doxycyclin STADA	doxycyclin	**106.32**	
X1	RGI Amoxicillin 500	amoxicillin	**102.50**	**amoxicillin**
X2	Letap Amoxicillin	amoxicillin	**125.69**	
X3	KAV Amoxicillin BP	amoxicillin	**	

* calibration curve of doxycycline was used

** sample was not able to be dissolved in the mobile phase

Samples for assay were prepared as follows:

10 tablets were weighed; crushed and approximately. 100 mg were transferred into a 100 ml flask and dissolved in the mobile phase. The solutions were sonicated for about 30 minutes to obtain maximum dissolution. Afterwards, each sample was filtered into a vial using a 22 µm sterile filter. Each sample was injected three times and average peak areas were calculated.

Assay: Contents of unit doses were calculated using the regression plot and the average weights of one tablet:

$$\text{content (mg)} = \left(\frac{\text{average peak area} - 105.15}{411.48} \right) \bullet \frac{\text{average weight}}{\text{dissolved sample in 100 ml}}$$

Impurities

Determination of impurities was carried out under the same conditions as assay, also using the same sample solutions. The injection volume was set to 50.0 µL. Signals were detected at 278, 272 and 254 nm compared via normalization of retention times. According to Ph. Eur. 6.0, the following impurities for ciprofloxacin are specified:

- Fluoroquinolonicacid (7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4- dihydroquinoline-3-carboxylic acid
- Ethylenediamine compound: 7-[(2-aminoethyl)amino]-1- cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3- carboxylic acid
- Desfluoro compound: 1-cyclopropyl-4-oxo-7-(piperazin-1- yl)-1,4-dihydroquinoline-3-carboxylic acid
- Decarboxylated compound: 1-cyclopropyl-6-fluoro-7-(piperazin-1- yl)quinolin-4(1H)-one
- 1-cyclopropyl-6-hydroxy-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid
- 7-chloro-1-cyclopropyl-4-oxo-6-(piperazin-1-yl)-1,4- dihydroquinoline-3-carboxylic acid .

- The exact identification of the specified impurities in the samples was not possible due to a lack of CRS reference substances.
- By normalization of obtained retention times according to Aksoy et al.[*], identification of impurities B (Desfluoro compound), C (Ethylenediamine compound), D (7-chloro-1-cyclopropyl-4-oxo-6-(piperazin-1-yl)-1,4- dihydroquinoline-3-carboxylic acid),

  E (Decarboxylated compound) and chloro– analogue was estimated (see table 9).

Table 8: Normalization of retention times (Rt) in ciprofloxacin samples for peak identification

X1				**X2**			
R_t	**Area [%]**	**Quotient**	**could be**	**R_t**	**Area [%]**	**Quotient**	**could be**
1.366	0.0216	0.212	solvent?	0.936	0.0587	0.146	solvent?
2.921	0.076	0.454	Impur E	1.345	0.0613	0.210	
4.606	0.1174	0.715	Impur C	2.942	0.067	0.459	Impur E
				4.615	0.2788	0.720	Impur C
				5.642	0.1233	0.880	
6.438	**99.785**	**1.000**	**Cipro**	**6.411**	**99.002**	1.000	**Cipro**
				7.98	0.3471	1.245	Impur D
				14.184	0.0614	2.212	Chloro-a.
X3				**X4**			
0.943	0.0356	0.147	solvent?	0.941	0.0472	0.148	solvent?
1.339	0.0174	0.209		1.377	0.0458	0.217	
2.933	0.0658	0.458	Impur E	2.889	0.0743	0.454	Impur E
3.428	0.0295	0.536		4.577	0.2956	0.720	Impur C
4.634	0.1696	0.724	Impur C	5.594	0.0858	0.880	
6.398	**99.6288**	**1.000**	**Cipro**	**6.359**	**99.141**	1.000	**Cipro**
14.183	0.0532	2.217	Chloro-a.	10.887	0.2456	1.712	
				14.047	0.0643	2.209	Chloro-a.

X5				**X6**			
1.369	0.0152	0.214	solvent?	2.934	0.0934	0.455	solvent?
2.935	0.0770	0.459		3.422	0.0369	0.530	
3.43	0.0363	0.537		4.613	0.1367	0.715	Impur C
4.622	0.0650	0.724	Impur C	**6.455**	**99.733**	1.000	**Cipro**
6.388	**99.7540**	1.000	**Cipro**				
14.073	0.0525	2.203	Chloro-a.				
X7				**X8**			
1.37	0.0878	0.211	solvent ?	0.943	0.0398	0.147	solvent?
2.925	0.0632	0.450		1.066	0.0252	0.166	
4.614	0.2479	0.710	Impur C	1.525	0.0396	0.238	
6.495	**99.1558**	1.000	**Cipro**	2.942	0.1025	0.459	
8.034	0.4453	1.237	Impur D	3.442	0.0698	0.537	
				4.642	0.1847	0.724	Impur C
				5.681	0.1415	0.886	
				6.411	**99.304**	1.000	**Cipro**
				14.353	0.0928	2.239	
X9							
1.081	0.0168	0.164	solvent?				
2.994	0.0327	0.455					
4.738	0.0873	0.720	Impur C				
6.578	**99.8632**	1.000	**Cipro**				

* Aksoy B, Kücükgüzel I, Rollas S (2007) Chromatographia 66:S57-S63

Table 9: Ciprofloxacin - normalization of retention times after Aksoy et al

Compound	Rt	RtCipro	Quotient
Ciprofloxacin	7.546	7.546	1.000
Impurity E	2.797	7.546	0.371
Impurity B	4.872	7.546	0.646
Impurity C	5.517	7.546	0.731
Impurity D	9.69	7.546	1.284
Chloro-a.	15.591	7.546	2.066

5.3.3.2. Doxycycline

The liquid chromatography system used for the determination of Doxycycline was the same as the one used for determination of ciprofloxacin. (Table7)

A reverse phase ODS C18 (2) column 250 mm × 4,6 mm, 5 µm particle size (Phenomenex Luna 5u) was used and maintained at ambient temperature (25° C). For UV-VIS detection, the wavelength was set to 350 nm.

The mobile phase was prepared as follows:

Millipore water, Acetonitrile and Perchloric acid were mixed (74:26:0.25) and pH was adjusted to 2.5 with 5 M NaOH. The chromatography was carried out under isocratic conditions with a flow rate of 1.0 mL min^{-1}. Injection volume was set to 10 µL for the assay method and 50 µL for the impurities method.

Calibration standards were prepared as follows:

For linearity and calibration, a stock solution of Doxycycline hyclate CRS was prepared (70.28 µg/ml) and diluted with the mobile phase to obtain final concentrations of 14.06, 28.11, 42.17, 56.22 and 70.28 µg/ml). Each sample was injected three times and average peak areas were calculated. The calibration curve was set up plotting obtained peak areas vs. concentration of ciprofloxacin; R^2 was calculated at 0.9904 (Fig 5).

Samples for assay were prepared as follows:

10 tablets were weighed; crushed and approximately. 100 mg were transferred into a 100.0 ml flask and dissolved in the mobile phase. The solutions were sonicated for about 30 minutes to obtain maximum dissolution. Afterwards, each sample was filtered into a vial using a 22 µm sterile filter. Each sample was injected three times and average peak areas were calculated.

Impurities

Determination of impurities was carried out under the same conditions as assay, also using the same sample solutions. The injection volume was set to 50.0 µL. Signals also were detected at 350 nm compared via normalization of retention times.

Doxycycline: According to Ph. Eur. 6.0, the following impurities are specified:

- 6-epidoxycycline((4S,4aR,5S,5aR,6S,12aS)-4-(dimethylamino)-3,5,10,12,2a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide),
- Metacycline((4S,4aR,5S,5aR,12aS)-4-(dimethylamino)-3,5,10,12,12a- pentahydroxy-6-methylene-1,11-dioxo-1,4,4a,5,5a,6,11,12a- octahydrotetracene-2-carboxamide),
- 4-epidoxycycline((4R,4aR,5S,5aR,6R,12aS)-4-(dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide)
- 4-epi-6-epidoxycycline(4R,4aR,5S,5aR,6S,12aS)-4-(dimethylamino)-3,5, 10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a, 5,5a,6,11,12a-octahydrotetracene-2-carboxamide.
- Oxytetracycline 2-acetyl-2-decarbamoyldoxycycline ((4S,4aR,5S,5aR,6R,12aS)-2-acetyl-4-(dimethylamino)- 3,5,10,12,12a-pentahydroxy-6-methyl-4a,5a,6,12a-tetrahydrotetracene-1,11(4H,5H)-dione).

Chromatograms of all samples showed a variety of additional peaks. As only reference retention times for Metacycline and 6-epidoxycycline were available, these two impurities probably can be identified at retention times of approximately 24.2 and 25.0 minutes (Graphic 1: Chromatogram below)Tetracycline and Metacycline were present in all samples, whereas 6-epidoxycycline

seemed only to appear in samples X4, X5 and X9. (Table7) percental peak areas of Doxycycline varied between 85.1 to 97.4 per cent

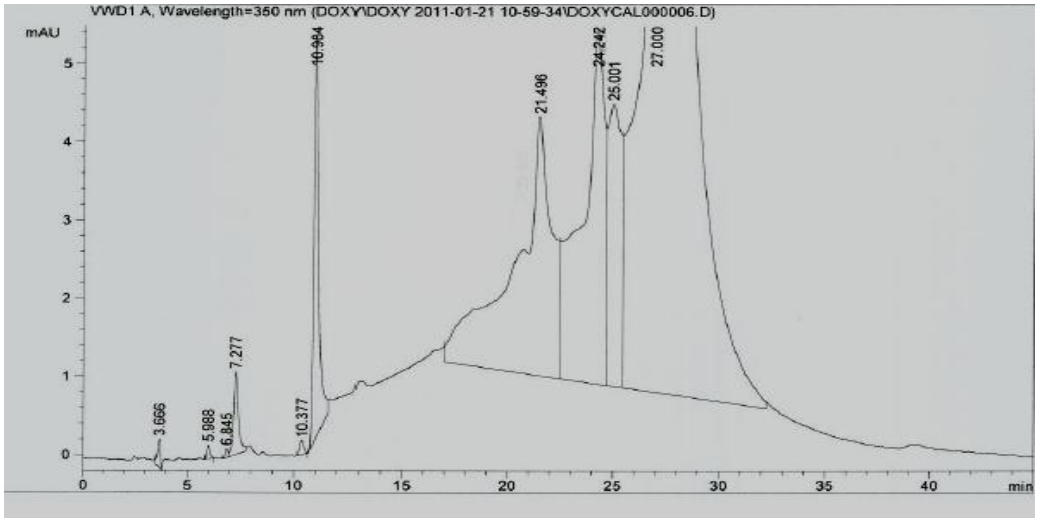


Figure 6: **Typical chromatogram obtained with doxycycline samples**

5.3.3.3. Amoxicillin

The liquid chromatography system used for amoxicillin was the same as the one used before.

Table.10: HPLC components for Amoxicillin

	Amoxicilline
Column	ODS C18 (2) column 250 mm × 4,6 mm, 5 µm particle size
Column temperature	35 °C
Detector	274nm
Injection volume	25 µL
Mobile phase	Phase A- 0.2 M potassium phosphate buffer pH 7.0 - Millipore water (5:5:90 v/v) Phase B: Methanol - 0.2 M potassium phosphate buffer pH 7.0 - Millipore water (50:5:45 v/v
Flow rate	1.0 mL min^{-1}

The column used also was ODS C18 (2) column 250 mm × 4,6 mm, 5 µm particle size (Phenomenex Luna 5u) operated at 35 °C.UV-VIS detection was carried out at 274 nm.

The mobile phase was prepared as follows:

Mobile phase A: Methanol - 0.2 M potassium phosphate buffer pH 7.0 - Millipore water (5:5:90 v/v).

Mobile phase B: Methanol - 0.2 M potassium phosphate buffer pH 7.0 - Millipore water (50:5:45 v/v).

A gradient elution was applied, with 5 % of mobile phase B for 5 minutes, then increasing at a rate of 2 % (B) to 65 % of B. Afterwards, decreasing at a rate of 8 % B to the original concentration.

A flow rate of 1.0 mL min-1 was maintained. Injection volume was set to 25 µL for the assay method and 50 µL for the impurities method.

Calibration standards were prepared as follows:

For linearity and calibration, seven stock solutions of amoxicillin trihydrate CRS in mobile phase A were prepared to obtain final concentrations of 0.25, 0.33, 0.40, 0.48, 0.66, 0.70 and 0.90 mg/ml). Each sample was injected three times and average peak areas were calculated. The calibration curve was set up plotting obtained peak areas vs. concentration of ciprofloxacin; R^2 was calculated at 0.9991 (Fig5).

Samples for assay were prepared as follows:

The content of 10 capsules was weighed; homogenized and approximately. 70 mg were transferred into a 100.0 ml flask and dissolved in the mobile phase A. The solutions were sonicated for about 15 minutes to obtain maximum dissolution. Afterwards, each sample was filtered into a vial using a 22 µm sterile filter. Each sample was injected three times and average peak areas were calculated.

Impurities:

Determination of impurities was carried out under the same conditions as assay, also using the same sample solutions. The injection volume was set to 50.0µL. Signals also were detected at 274 nm compared via normalization of retention times.

Amoxicillin

According to Ph. Eur. 6.0, the following impurities are specified:

- 6-aminopenicillanic acid:
  (2S,5R,6R)-6-amino-3,3-dimethyl-7-oxo-4-thia- 1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

- L-amoxicillin:
  (2S,5R,6R)-6-[[(2S)-2-amino-2-(4-hydroxyphenyl)- acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylic acid.

- Amoxicillindiketopiperazines:
  (4S)-2-[5-(4-hydroxyphenyl)-3,6-dioxopiperazin-2-yl]-5, 5-dimethylthiazolidine-4-carboxylic acid.

- Penicilloic acids of amoxicillin:
  (4S)-2-[[[(2R)-2-amino-2-(4-hydroxyphenyl)- acetyl]amino]carboxymethyl]-5,5-dimethylthiazolidine-4-carboxylic acid.

- Penilloic acids of amoxicillin:
  (2RS,4S)-2-[[[(2R)-2-amino-2-(4-hydroxy- phenyl)acetyl]amino]methyl]-5,5-dimethylthiazolidine- 4-carboxylic acid-3-(4-hydroxyphenyl)pyrazin-2-ol

- D-(4-hydroxyphenyl)- glycylamoxicillin:
  (2S,5R,6R)-6-[[(2R)-2-[[(2R)-2-amino-2-(4-hydroxy- phenyl)acetyl]amino]-2-(4-hydroxyphenyl)acetyl]-amino]- 3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]-heptane-2- carboxylic acid.

- (2R)-2-[(2,2-dimethylpropanoyl)amino]-2-(4- hydroxyphenyl)acetic acid (2R)-2-amino-2-(4-hydroxyphenyl)acetic acid.
- co-oligomers of amoxicillin and of penicilloic acids of amoxicillin oligomers of penicilloic acids of amoxicillin.
- 6-APA amoxicillin amide: (2S,5R,6R)-6-[[(2S,5R,6R)-6-[[(2R)-2-amino-2-(4- hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1- azabicyclo[3.2.0]heptane-2-carbonyl]amino]-3,3-dimethyl- 7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

5.4. Findings

All products tested passed the tests for identification of active ingredients indicating that the worst case of counterfeiting involving wrong active ingredients was not found.

Ciprofloxacin samples complied with the specifications for assay in the European Pharmacopoeia. Labeled active ingredients were identified in all samples, however with varying dosages. Six of the nine (X_2,X_3,X_4, X_6, X_7,X_8 in table 7) Doxycycline samples analysed did not comply with the pharmacopoeial requirements of 95–105%:

Impurity determination was tried to be carried out via normalization of retention times of obtained chromatograms (see table 2), but conclusive allocation was not always possible.

Impurities D and E (decarboxylated analogon) has been most likely present in all revised samples, but regarding other impurities, distinctive determination was not possible, though they also are present in every sample.

When scoping the percentages of areas of these peaks, it is clear that, although impurities may be present, they aggregate to a very small rate.

Unknown peaks, especially in Doxycycline measurement, may stem from beginning degradation of the active ingredient (epimerization, dehydratation, inactivation by means of reactions due to used excipients). As a non-pharmacopoeial method (Skulason, Ingolfsson: “Development of a simple HPLC method for separation of Doxycycline and its degradation products” Journal.

Pharm. and Biomed. Analytics, 33(2003) 667-672) was used for analysis, the results also have to be regarded with reserve.

Differences in the amount of active ingredients may also result from bad manufacturing habits (inaccurate weighing or filling of capsules) or bad storage conditions, either from the side of the manufacturer or during the way to the laboratory.

For Amoxicillin, no reference retention times with these chromatographic conditions were available at all. Sample X1 and X2 show similar peak patterns, especially at 3.1, 4.7, 5.2, 21.1, 23.4, 25.2 and 27.1 minutes retention times. Percentage of the amoxicillin peaks were from 91.1 to 91.2 per cent. (Chromatogram below)

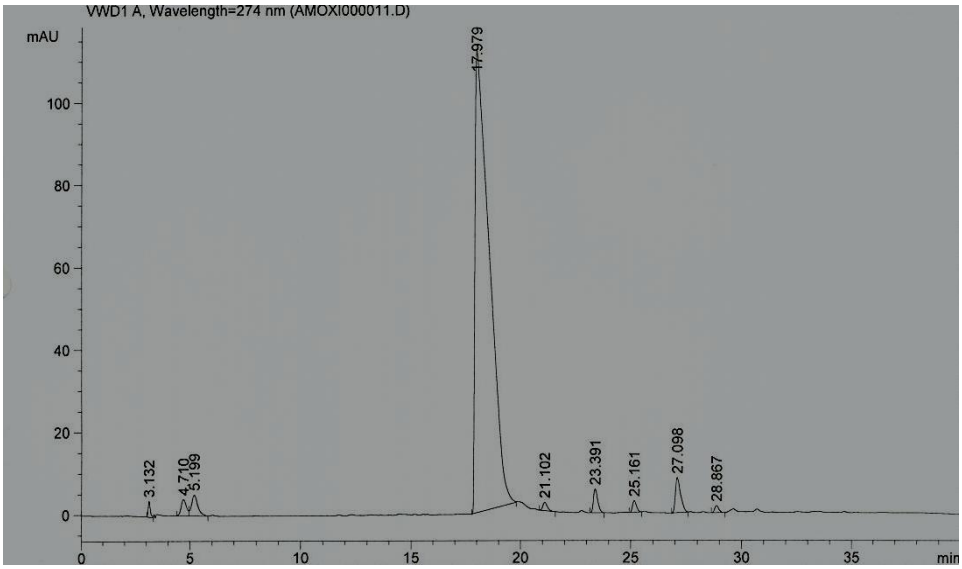


Figure 7: Chromatogram of Amoxicillin sample.

PART 4: RESULTS

CHAPTER VI: Summary of Quality Failures

Although the sample size in this study was small, it provides an indication about the availability of counterfeit /substandard antibiotics in Africa. Poor-quality medicines particularly affect lower-income countries, where inadequate infrastructure, non-regulated drug outlets and black market operations make drug quality surveys difficult. Drug regulation and information enforcement are scant. Patients may buy all types (OTC and Prescription Only Medicines) without consulting physicians. Taking in consideration 17 medicine sellers visited, in common practice, Patent Medicine Vendors (PMV) in Nigeria or Licensed Chemical Shops (LCS) in Ghana behaviors are:

69% selling the requested medicine,

30% giving their own suggestions to the customer,

19% asking questions about the illness, and

21% providing instructions on how to take the medicine.

Thus the major role of the LCS or PMV appeared to be just one of salesperson. Rarely, medicine sellers ask customers about their illness. Sellers with many years of experience do not sell immediately. They look at the customer's attitude, the way he asks about the medicine in order to be sure that the customer is not from a regulatory body. Thus, according to the sort and quantity you want to buy, either you get it directly from the counter or you should wait until he/she brings it from the storage room which – usually – is up to five hundred meters away from the point of sales. For the security of their transaction, illicit vendors do not allow all their customers to know where they store their goods. In the case the seller is sure his/her customer may not be a trouble maker (not from regulatory authority) he/she takes the customer to the storage point. Fortunately, I had a chance to be taken to such a storage room. It was wonderful. The room was full of not only medicines (solid and liquid forms) from India, China and Singapore, but also of many sorts of medical devices and medicinal products manufactured or distributed by locally authorized manufacturers and distributors. There was no air condition to keep the temperature acceptable (ambient). I encountered this type of procurement places in

Lagos (Muhsin, Surelere, Agege), in Abidjan (Adjame Rossi), Lomé (Assiganme) and Cotonou (Dan Tokpa). There, you could see even medicines from Western countries.

In official pharmacies in the respective survey countries, the service seems to be the same. Antibiotics are sold as OTC (over the counter) drugs in a single blister without package leaflet or in a small nylon bag according to the patient financial input. Physician's prescription is not a must. "Most antibiotics are in the national Essential List*, that is why antibiotics are sold free of prescription," said an employee in one pharmacy, but regulatory authorities in Ouagadougou (Burkina Faso) deny this statement. In a regular pharmacy in Ouagadougou (Burkina Faso), an employee receives the prescription (if any), brings the prescribed or requested medicine to the desk. Mostly, the one who takes the medicine from shelves is not the one who hands over medicine to the customer at the POS (Point of Sale); at the point of sale, it is generally a close relative of the pharmacist without any pharmaceutical training background, serving just as cashier. In all pharmacies I visited, the procurement of medicine in single blister form or retailed tablets and capsules enclosed in small plastic bags was more frequent although there were no instructions about side effects or any warning on storage to the patient. No matter if the patient is old, too young or illiterate. All of these practices permit the itinerant hawkers and illicit sellers to say that the only difference between their service and registered pharmacies is the price and since they are cheaper, the patients prefer to come to them. Most of the illicit sellers ignore that under high heat and humidity the medicines they are selling are degraded, some rely only on the expiration date printed on blister to ensure the quality to the consumer.

These Primary Medicine Vendor or Licensed Chemical shop roles can be enhanced through education, training and policy changes to standardize and legitimize LCS, PMV contributions to primary health care. This has been done in Ghana. The Ghanaian Pharmacy Act 489 from 1994 permits the Pharmacy Council to license individuals as chemical sellers but does not specify any educational level as a requirement for licensure. However, the Pharmacy Council has set

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* Essential List: The WHO has settled a list of ''drugs that satisfy the health care needs of the majority of the population; they should therefore be available at all times in adequate amounts and in appropriate dosage forms, at a price the community can afford."

the O-Level (Ordinary Level: a senior secondary school certificate or high school certificate) as the minimum qualification*. Despite this standard, some licensed chemical sellers are complete illiterates. The appearance of Licensed Chemical Shops and pharmacies is much alike. Some Licensed Chemical Shops even look more attractive than pharmacies. The difference between an LCS and a pharmacy is the description (writing) in front of the building. For Licensed Chemical Store the law does not specify the educational level of the seller/distributor. In pharmacies you may find a graduated pharmacist. In Ghanaian law, pharmacies are permitted to dispense or sell all kinds of medicines whereas licensed chemical stores are authorized to sell only OTC (Over the Counter) drugs.Selling medicine is a business with tentacles in all corners of Africa where people perceive a need to buy medicinal products. In this context, the PMV can be broadly defined as a person without formal pharmacy training who sells orthodox pharmaceutical products on a retail basis for profit.

Price differentials create an incentive for drug diversion within and between established channels. There is a lack of effective intellectual property protection and due regard is not paid to quality assurance. Parallel trade in pharmaceuticals generates a number of monitoring difficulties that are less apparent but significant threats to safety. With drugs entering through porous borders, safety warnings and product recalls are more difficult to execute. In addition, product-packaging standards vary across markets and prescription recommendations as well as contraindications also may differ. Differences in product packages remove the familiar packaging clues that are important in the visual detection of counterfeits. Parallel trade results in unregulated distribution pipelines and weakened regulatory control of the supply chain, both of which are characteristics that facilitate counterfeiting.

The local industry desperately needs support via capacity building in order to enable them to meet the required quality standards. The quality testing study outcomes suggest the need to enhance the quality of medicines on the market.

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* Training and Accreditation standards. Available from www.pharmacycouncilghana.org;accessed on February 23rd 2010

PART 5: DISCUSSION, CONLUSION AND RECOMMENDATIONS

CHAPITER VII: Discussion

We acknowledge that a broad review of quality assurance of medicines over an expansive and complicated area such as Africa is a challenge. As it appears from our review, there is few data on which to judge drug quality, as few objective studies have been conducted in Sub-Saharan Africa. A clear distinction needs to be made between counterfeit and substandard products. There is tendency in the literature to use the two terms interchangeably as highlighted by Shakoor*et al*[78]. The WHO defines counterfeit products as "*...those deliberately and fraudulently mislabeled with regard to identity and/or source...*"[79] Whilst it is the case that most counterfeit products are sub-standard, there are some that are within the specified pharmacopoeial limits as shown by Atemnkeng et al in the DR Congo [80].The review showed that in Africa most products are sub-standard and not counterfeit[81], pointing perhaps to lack of enforcement of Good Manufacturing Practices (GMP) rather than a deliberate attempt to defraud. Drug action is such that a minimum concentration is required to elicit a physiological response (lowering of elevated blood glucose levels in diabetes mellitus for instance) or killing parasites in the case of infectious diseases .Sulfadoxine and Pyrimethamine tablets exhibit notoriously poor in-vitro dissolution profiles, especially with regard to the Pyrimethamine component. This is mostly a problem with the generic products rather the originator. It is thought that this is due to the poor aqueous solubility of Pyrimethamine occasioned by the use of poor quality raw materials or poor choice

[78]Shakoor O, Taylor RB, Behrens RH. "Assessment of the incidence of substandard drugs in developing countries". Tropical Medicine and International Health. 1997;2:839–845.available from http://www.ncbi.nlm.nih.gov/pubmed/9315042 ;Internet accessed on August 12th, 2010

[79] WHO Counterfeit drugs: guidelines for the development of measures to combat counterfeit drugs. Geneva: 1999. pp. 1–60;available from http://jac.oxfordjournals.org/content/60/2/214.full.Internet accessed November 27th,2009

[80]Atemnkeng MA, De Cock K, Plaizier-Vercammen J. "Quality control of active ingredients in artemisinin-derivative antimalarials within Kenya and DR Congo".Tropical Medicine and International Health. 2007;12:68–74 available from www.ncbi.nlm.nih.gov/pubmed/17207150; Internet accessed December10th,2009

[81]Amin AA, Snow RW, Kokwaro G O. "The quality of sulfadoxine-pyrimethamine and amodiaquine in the Kenyan retail sector". Journal of Clinical Pharmacy and Therapeutics. 2005;30:559–565;available from www.ncbi.nlm.nih.gov/pubmed/17207150 Internet accessed on June 18,2010

of excipients in the formulation.[82,83]. The pharmacopoeia assumes a good in vitro-in vivo correlation such that a product which failed in vitro dissolution will most likely fail in an in vivo (bioavailability) test and therefore result in a low plasma level of Sulfadoxine and Pyrimethamine with the attendant risks of therapeutic failure. The few studies done here are inconclusive as they have been faulted on sample size requirements due to restricted budget.

However, in the case of the Artemisinins, which are used as first-line therapeutics in at least 30 Sub-Saharan countries[84], the incidence of counterfeit Antimalarial drugs is increasing. The basis for this assumption is that these high value products are consumed by millions of Africans each year and therefore represent a profitable business opportunity. Ensuring the quality of medicinal products is important throughout the whole distribution chain, storage and dispensing outlets. A very good drug that leaves the factory gate might well be worthless a few months later due to rapid deterioration as a result of exposure to excessive moisture and temperature at the point of sale. This has serious implications for the ACTs which are the favored first-line Antimalarial for most of Sub Sahara Africa. The Artemisinins are hygroscopic and have a short shelf life of 36 months or less. It is imperative to study how these drugs hold up under typical storage and handling conditions in the tropics as they probably constitute the latest effective drugs against the lethal Plasmodium falciparum malaria.

What remains is how the ECOWAS ´States can collectively leverage economies of scale to the mutual benefit to address access and quality concerns. However, tighter enforcement of some regulations could have a negative on public health. Eliminating all prescription only medicines (POM) from drug stores could restrict the access of poor rural populations to effective medicines, particularly where government facilities or formal pharmacies are out of reach.

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[82]Risha PG, Shewiyo D, Msami A, Masuki G, Vergote G, Vervaet C. “In vitro evaluation of the quality of essential drugs on the Tanzanian market”. Tropical Medicine and International Health. 2002; 7:701–707. [PubMed]. Internet accessed on June 19, 2010.

[83]Kibwage IO, Ngugi JK. “Sulphadoxine/Pyrimethamine tablet products on the Kenyan market: quality concerns”. East and Central African Journal of Pharmaceutical Sciences. 2000;3 :14–19,cited in Health Action International (HAI) Antimalarial Medicines in Kenya; available from http://apps.who.int/medicinedocs/documents/s16424e/s16424e.pdf.Internet accessed on October23,2011

[84] Amin AA. Range “Quality and costs of antimalarial drugs available in the retail sector in Kenya”, available from http://www.kemri-wellcome.org/dissertations/Phd_2005_Amin_A.A.pdf.Internet accessed October 2011.

This would inevitably drastically reduce drug availability in rural areas. Enforcing the regulation that only drugs in unit packs should be sold over-the-counter has the potential to guard against tablet contamination and degradation, and to improve labeling and dosing instructions, which in turn has been demonstrated to improve treatment adherence (WHO 2004). However, this could substantially increase the cost of pharmaceutical products. For example packaged Sulfadoxine

Pyrimethamine (SP) was on average 1.8 times the retail price of loose SP tablets (Goodman 2004). Although packaged drugs may be perceived as better quality, such an increase in price would run the risk of further reducing the proportion of patients who purchase an adequate antibiotic dose.

CHAPTER VIII: Conclusion and Recommendations

8.1. Conclusion

Problems concerning drug safety and efficacy are generally caused by drugs containing toxic substances or impurities, substandard preparations or counterfeits. All of these problems can be tackled effectively only by establishing an effective drug regulatory system. It is very clear to all healthcare professionals that a major source of substandard products in Sub-Saharan Africa is the multitude of unregulated drug markets in major cities. These unregulated markets have existed since the 60's in rural areas which have never been penetrated by official pharmacies and have grown in number and complexity over the years with globalization. Medicines peddlers and medicinal products on market stall have survived the efforts of various governments to forcefully dismantle them, which never succeeded, but rather ended up in life attempt against national health authorities.For a great proportion of the developing countries, health conditions are worsening, perspectives for improvement are not encouraging and without a fundamental change in the pharmaceutical market supported by a strong political will, the slogan "health for all" will not come to fruition in the near future. I could observe during my research survey that all West African countries are commonly facing the ravages of infectious diseases and nowadays cardiovascular diseases and diabetes. Adopting individualistic approaches in sourcing essential medicines, the countries lose the one leverage (influence) that could have been utilized through a pooling of regional resources. Shall ECOWAS countries use a data to select which drugs actually could address the largest proportion of diseases that commonly affect the region, subsequently all countries could engage themselves in the so called "pooled procurement" by which all

West African states identify their medicine needs and identify the supplier that offers the best competitive pricing and quality terms. In this scenario stakeholders would no longer negotiate with separated, local health agencies such as Ghana Food and Drugs Board or Directorate for pharmacy, laboratory and medicine devices from Togo but with a single entity representing the whole of West Africa standing together. How to ensure that medicines entering in ECOWAS are of the required standards? The network should be based on an approach of shared responsibilities among the participating states; e.g. Ghanaian regulatory body: the Food and Drugs Board (FDB) and Cote d´Ivoire ´s DPLM (Direction des Pharmacies Laboratoires et du Médicament) may ensure a common harmonized pharmaceutical regulatory system to achieve international Good Manufacturing Practice standards, while Nigeria ´s NAFDAC takes care of post marketing surveillance. Hopefully this means that only drugs of a certain standard gain access to regional market and hence to patients. The economic burden of expensive drugs which may not be feasible for a single country might be addressed by a conglomerate of ECOWAS countries resolved to ensure access to quality drugs for their entire population. Could West African States thus consider a future of shared roles and responsibilities, where Liberia and Benin do post-market surveillance for Antimalarials, Nigeria sorts it out for Antiretrovirals while the Gambia and Senegal do same for all Antituberculotic drugs on the West African market? The last area worthy of collaboration is that of building the human capacity of local pharmaceutical industries and quality control laboratories to meet prequalification standards. With such a commitment, there shouldn’t remain any obstacles which could prevent the West African States from manufacturing medicines of the highest quality in order to meet the regional collective needs. Drug regulatory authorities should foster regular communication with local manufacturers. They should also acknowledge the right of citizens to be provided with accurate and appropriate information on drugs marketed in their country. Educating citizens about the efficacy, safety, quality and rational use of drugs will ultimately enhance the achievement of regulatory objectives.

A regional harmonized medicine regulatory authority promises the following advantages for the Pharmaceutical sector and public health in general:

- One umbrella for all manufacturers, importers and distributors in each ECOWAS country. Local manufacturers will also gain immensely in the area of capacity building and utilization of countries networking.
- The manufacturers and consumers will enjoy the economy of scale (which remains the only attraction to the illegal markets) in a sanitized, well-regulated and controlled environment.

- Full involvement of trained pharmacist at every point of ethical drug distribution combined with effective regulation, ensure the availability of quality and safety of pharmaceuticals for the consumer.

  - An environment easier to regulate and control.
  - The various regulatory Agencies will therefore enjoy more cooperation and the resultant synergy in their activities.
  - The sanitized system will make it impossible for criminals to find their way into drug trade channels, since there has to be a thorough screening before anyone is accepted into the regional market.
  - Combating health workforce shortages and poor work environments is critical, requiring the planning and implementation of comprehensive and integrated approaches without delay.

    Training, sustaining and retaining a motivated and supported workforce will require long-term commitment, structural and fiscal changes, and partnerships at country, regional and international levels. Developing effective policies and strategies for the retention of health personnel, such as the review of salaries and implementation of incentive schemes and the strengthening of human resources planning and management will enhance the workforce.

    At international level, it's necessary creating synergies through communication, collaboration and cooperation. Support regional harmonization initiatives by sharing experience from harmonization processes and providing expertise in support of harmonization.

Support participation of regulatory staff in harmonization initiatives such as the African Medicine Regulation Harmonization Initiative (AMRHI)[85].

Encourage the process of implementation good quality management system. With a long term vision, assurance of equivalent approach to manufacture and control of medicines, authorization and supervision of clinical trials, as well as frequent controls in procurement and retail outlets. Focus on where products are made and tested. Provide opportunities for training of drug quality control laboratory staff to improve quality testing skills and support/partnering with local manufacturers to transfer appropriate technology, human, equipment and technical knowhow to produce quality essential medicines locally at reasonable costs.

[85]"African Medicines Registration harmonization Initiative (AMRHI) summary status and future plan". available on http://drop.io/AMRH_Internetaccessed on April 23rd,2011.

Adjust prices of medicines intended for low income countries-to local financing reality and apply specific labeling to prevent their re-entry into the Western market e.g. ARV (Antiretroviral) drugs against Human Immunodeficiency Virus HIV.

Develop affordable appropriate technologies; suitable, reliable, and less time consuming analytical methods and tools for monitoring the quality of medicines in the market e.g. portable minilabs, Raman Truscan. Support establishment of regional Bioequivalence centers that will conduct studies at reduced cost for medicines manufactured locally.

In order to sanitize the drug distribution channels, the permanent dismantling of illegal markets is of paramount importance. To this end the WAHO (West Africa Health Organization) proposed the concept of regional harmonized drug regulation and distribution[86]. For any pharmaceutical to satisfy the legal requirements of any ECOWAS country into which it is imported, consideration should be given to the pre documentation approval such that clearance is provided prior to arrival of any medical consignment . Whilst importation regulations vary from country to country, below are the regulations which NIGERIA provided as an example.

(a) There must be evidence of registration of the product in the country of the manufacturer i.e. product license /Certificate of registration

(b) There must be evidence by the competent health authority that the sale of the product does not constitute a contravention of the drug laws in the manufacturer´s country, e.g. Certificate of Pharmaceutical Product (COPP) that conforms to WHO format.

(c)The documents in respect of (a) (b) shall be authenticated by Nigerian Mission in that exporting country.

The whole objective is to create an ordered network for the regulation sale and distribution of wholesome pharmaceutical products under the supervision of one regional health institution. Entry of pharmaceuticals into the ECOWAS market will be controlled and restricted to drugs

[86]"The impact of ECOWAS in the implementation of the pharmaceutical manufacturing plan for Africa"; available in Brief for the Implementation of the Pharmaceutical Manufacturing Plan for Africa (PMPA), Ndjamena, Chad, 13-17 June 2011.

that have satisfied all WAHO requirements for safety and efficacy. When the regional medicines regulatory bodies have been put in place and are being managed by duly authorized people, professionals will surely opt to patronize them. WAHO can then proceed to demobilize the existing unregulated open markets. This will diminish the current need for existing illegal markets and will make it easier for national health authorities and law enforcement agencies to close down such markets. In such circumstances, the social impact of the closures will be minimized and the chances of getting local governments involved in the exercise will be enhanced. A clear sense of duty on the part of employees is important if regulatory processes are to be pursued consistently.

Regulatory processes should be systematically monitored in order to identify problems and determine whether the actual activities match the intended actions. Ensuring the safety, efficacy and quality of drugs available to the public is the main aim of drug regulation. If regulatory goals are to be achieved, appropriate structures must be established and appropriate activities carried out to achieve the desired goals.

We believed that a similar study involving a bigger number of countries representing different levels of development would provide deeper insight into the strengths and weaknesses of drug regulatory authorities and the different strategies used to improve drug regulation performance.

8.2. Recommendations for Effective Drug Regulation.

Every regulatory action contributes to ensuring the safety quality and efficacy of drugs. A clear sense of the mission of the regulatory authority is important in motivating DRA staff to pursue regulatory processes in order to achieve drug regulation. This study found that there was a high prevalence of poor quality drugs. The findings provide areas for public intervention to improve the quality. The regulatory capacity of the whole ECOWAS region in the area of post market surveillance needs to be strengthened by training more field inspectors and boosting the testing capacity (equipment and logistics) of the Quality Control Laboratory.

The collaboration between all pharmaceutical stakeholders, the WHO and their funding partners such as World Bank needs to be strengthened to improve national medicines quality assurance infrastructure in the interest of public health and safety.

There should be enforced checks and regulation of drug supply management as well as stricter penalties for people stocking substandard and counterfeit drugs. Self-assessment can help an organization to learn about its own strengths and weaknesses. Transforming each Drug Regulatory Authority (DRA) into a learning organization which routinely conducts self-assessment and continuous quality improvement can be a powerful approach to enhancing drug regulatory performance. Systematic evaluation allows an objective and comprehensive appraisal of performance and identification of strengths, weaknesses and measures for improvement. Regular evaluation enables a DRA to learn continually about the quality of its performance, and to develop awareness of any positive or negative changes in that performance. This involves setting up mechanisms for mutual review of drug regulation systems. It serves as a means of external auditing (peer review), whereby the performance of one agency can be compared with that of others. Comparing The NAFDAC and the Burkina Faso quality control laboratories with the Kenyan WHO prequalified MEDS (Mission for Essential Drugs Supply) quality control laboratory is an example. Proficiency tests are performed by the participating laboratories in such a way that each laboratory learns how well it is performing in comparison with the others[87].

To overcome human resources problems, coordination may be established between the DRA and the country's educational institutions, to provide the number and types of pharmaceutical competency which are needed. The aim is to develop skills through short training courses. A coherent, module-based educational package like the one initiated since autumn 2010 by the West Africa Health organization (WAHO) may be developed by collaboration between countries. Since drug regulation involves various stakeholders with commercial interests who may try to exert pressure on the authority in order to secure decisions in their favor, health authorities should employ people with the specialized knowledge and skills required to ensure effective drug regulation. Employees must be individuals of integrity and should be well remunerated.

Health insurance through basic but strong mutuality and prescription drug coverage, will address an affordable health system. Manufacturer’s price dumping, this alternative would require

[87] Sauwakon Ratanawijitrasin, Eshetu Wondemagegnehu. “Effective drug regulation- A multicountry study”. A book published by World Health Organization 2002 WHO Library Cataloguing-in-Publication Data ISBN 92 4 156206 4 .

pharmaceutical manufacturers to change their pricing policies in existing low-price countries. Prices would increase to a uniform price level, but manufacturers would offer rebates that would be aid to the payer or national health system. Drugs consumed domestically in low-price countries would be subject to government price controls, while exported products would be priced according to market forces. It should be possible to institute this pricing policy through contractual agreements between manufacturers and suppliers.

The essential drugs concept is evidence based, simple, promotes equity, and is firmly rooted in public health principles.This strategy is a proven success but it needs to be strengthened, and new ways of implementation have to be explored, given the changing context.

CHAPTER IX: References

9.1. Annexes

Annex1: Compilation of NAFDAC List of some identified fake products (From October 2001-December 2005)

Identity of faked Item	Difference(s)	
	Genuine	Fake type
Ampiclox Capsules 500mg® By SmithKline Beecham	Ampiclox® Capsules 500mg By SmithKline Beecham Contains labeled content of active ingredient. Registered by NAFDAC, Registration #04-0181	.Amcilox 500 caps® Made in India by Dotsy Pharmaceuticals P.Ltd, Phase II.Extn .Nodia 201.301 Very low content of active ingredient
Ciprolex® Ciprofloxacin Tables USP 500mg	Ciprolex®: Ciprofloxacin Tablets USP 500mg Manufactured for: London United Exports Ltd London NW4 England. By AGLOWMED Ltd.A1-6104/2 GIDC INDIA There are holograms on both blister and protective foils. Registered by NAFDAC Registration # 04-2719	CIPROLEX®: Ciprofloxacin Tablets USP 500mg.Manufactured for LONDON UNITED PHARMACEUTICALS LONDON ENGLAND. No name and location address of manufacturer. There is no hologram on packet and the product does not have protective foils. Not registered by NAFDAC
Sulfadoxine & Pyrimethamine Tablets	Several registered brands	MALARIGO® (Sulfadoxine &Pyrimethamine Tablets UST) 3tablets Exported by AMARDAHAN TRADERS & EXPORTERS PVT:LTD Sarigam 396 155,Dist.Valsad Not registered by NAFDAC

Doxycycline Capsules	Vibramycin® Capsules: Doxycycline 100mg Has only English wording on the package .Manufactuered by Pfizer Products,Plc 1 Henry Carr Street Ikeja – Lagos. NAFDAC Registration No. 04-0552	**1.** DOXYCYCLINE CAPSULES 100mg. Has English and Arabic inscription on the pack. Manufactured by TABROS PHARMA; L 29/B Sector 22 FB Industrial Area Karachi 75950 Pakistan Not registered by NAFDAC. **2.** Monodox® 100mg 10stuck Merckle GmbH; Blaubeuren BDR. All wording on package and instruction leaflet in German language. Not registered by NAFDAC

Source: NAFDAC Bulletin 2001-2005.

Annex 2: Samples collected in Lagos, from 19th to 22th January 2010

Brand Name	Active Substance/Strength	Manufacturer/ Distributor	Procurement Site/Date	Concerns
Cenox®	Ciprofloxacin 500mg	Elbe Pharma Nigeria Ltd.	Pharmacy and Stores Ltd. IyanaIpaja Lagos/Jan.21,2010	Product with two different addresses. Registered by NAFDAC under 04 3002 in the current register (first edition) Green Page with location in Plot 1 M/M Int'l Airport Isolo Lagos; but the outer package carries a different address: Elbe PharmaIkoyi, Lagos
Chlomacol®	Chloramphenicol BP.250mg	Yangzou No.3 Pharmaceutical.Co Jiangsu -China/ Distributed by Geneith Pharmaceuticals	Kech Pharmacy & Stores Ltd. Ekoro Road AbuleEgba, Lagos/ January 21.2010	Chlomacol®. has NAFDAC Reg.No. 04-3729 . On the homepage of Geneith global Pharm, Chlomacol is registered under NAFDAC Reg. No.04 3481. Labeling information is inadequate. The samples I bought in Kech Pharmacy Lagos with NAFDAC Reg.No. 04-3429 have the following information on their package leaflet: Contraindication: "Children fewer than 8 years or age should not be treated." Dosage and administration: "Children in dose of 25 to 50mg/kg 3-4 times daily."
Durban250®	Choramphenicol 250mg	Greenfield Pharmaceutical Jiang Su PR China	Lagos/ January 19, 2010	Inadequate labeling (readability); text not legible not clear and easy to read.

Brand Name	Active Substance/Strength	Manufacturer/ Distributor	Procurement Site/Date	Concerns
Labcin500®	Erythromycin 500mg	Embassy Pharmaceutical and Chemicals Ltd. Lagos	Cool United Pharmaceutical Onimaya-Road Agege.Lagos	The information on the package leaflet are not complete, incorrectly written and meaningless (Special Precautions, Pregnancy, Lactation, Eldery). The labeling "For Medical/Pharmacy Professional Only" is not written on the out-package. Despite all, LABCIN500 is registered in NAFDAC's current fifteenth edition Green Page under NAFDAC Reg.No. 04-6174
RGI Amoxicillin500®	Amoxicillin 500mg	RichyGold International Ltd. Oshodi-Lagos	Rome Park Enterprises, off Ojuwoye Market Mushin,Lagos/ January 22,2010	Labeling not easy to understand (contraindication)
CIPROVAM® 500	Ciprofloxacin 500mg	TuyilPharm.INDIA .LIMITED	ZomezConcern (NIG) Agaran Street, Mushin,Lagos January 22,2010	Both outer package and labeling carry 22 New Yili-Road Ilorin Nigeria; but the address on the blister is: 22, Stadium Road Ilorin Kwara State Nigeria
Erythr®500	Erythromycin 500mg	JiansuRuinianQianj in Pharmaceutical Jiansu Province China/ VIXA Pharmaceutical Co. Ltd. Ogudu, Lagos	Lagos	The brand name on the blister is Erythr instead of Erythr500; NAFDAC Reg.No. is A4-2338, usually 04, not A4; and the Erythr500 is not registered in NAFDAC's current Green Page
Lampicin®	Ampicilin 250mg	Me Cure Industries Ltd. Oshodi, Lagos	Mushin Market date: January 22, 2010.	Inadequate and unclear labeling of the leaflet. Self life: Two years from manufacturing date and one year from expiration date; dosage is written incorrectly

Brand Name	Active Substance/Strength	Manufacturer/ Distributor	Procurement Site/Date	Concerns
Quintor®500	Ciprofloxacin 500mg	Torrent Pharmaceutical Ltd. Distr. Mehsana India	Jan AbuleEgba Clinic, Lagos January 20, 2010	Inadequate and unclear labeling of the leaflet. Self life: Two years from manufacturing date and one year from expiration date; dosage is written incorrectly
Ucillin®250	Ampicillin 250mg	Greenfield Pharmaceutical Jiang Su Co.Ltd India	Ilupejo Lagos/ January 22,2010	Both outer packaging and leaflet are addressed 15, Wilmer Street Off town planning way Ilupeju Lagos, but in the national register (Green Page), 8, Ipaye Street, Aguda, Surulere Lagos

Annex 3. Samples collected in Burkina Faso: January 30 to February 10, 2010

Most medicines are sold in a single blister without packaging or information leaflet. I asked in a formal selling point (Yaldago Hospital Pharmacy) why such a practice, and I was told that patients are supposed to know what they are buying and that many of them are under treatment by a physician and were advised which medicines to buy. Here, the seller who is supposed to be a professional sold some antibiotics to me without prescription and showed me on a computer screen that Erythromycin, Amoxicillin and Ciprofloxacin are sold without physician's prescription.

The following medicines have been collected in single blister form:

Brand Name	Active Substance/Strength	Manufacturer/ Distributor	Procurement Site/Date	Concerns
Amoxicillin 500mg	Amoxicillin 500mg	Strides Arcolab Limited Bangalore-India	Yaldago Hospital Pharmacy, Ouagadougou February 2, 2010	Amoxicillin 500mg is sold in single blister form in an ordinary pharmacy without user information leaflet

Brand Name	Active Substance/Strength	Manufacturer/ Distributor	Procurement Site/Date	Concerns
Ampicillin 500UBI	Ampicillin 500mg	Ubigen	Pharmacy Diawara Ouaga February 10, 2010	Amoxicillin 500mg is sold in single blister form in an ordinary pharmacy without user information leaflet.
Erythromycin 500mg	Erythromycin 500mg	Bristo-Myers Squibb.	Yaldago Hospital Pharmacy, Ouagadougou February1, 2010.	Single blister sold in ordinary pharmacy without package leaflet
Ciprofloxacin 250mg	Ciprofloxacin Hydrochloride o,25g	Chinese Drug Store Ets. Yan Yan Rue Patrice Lumumba	Ets Yang Yang January31, 2010	Sold in general store where all articles including food stuff ,shoes are from China, labeled in Chinese language
Ciprofloxacin 500mg	Ciprofloxacin 500mg	Pharmacy de la poste BP.2829 Ouagadougou	Pharmacy de la poste BP.2829 Ouagadougou February 6, 2010	Ciprofloxacin sold in blister without Patient information leaflet.
Metronidazole 0,2g	Metronidazole 0,2g	Illegible(labeling in Chinese language)	Ets. YangYang. Rue Patrice Lumumba January31, 2010	labeled in Chinese language in a French speaking country. The store holder does not speak either local language or French.
Maloxine	Sulphadoxine USP 500mg Pyrimethamine USP 25mg	Schreechem Laboratories Bombay 400083.under licence from Exphar SA Belgium	Ets. YangYang. Rue Patrice Lumumba January 31, 2010	The forensic test with TruScan in Germany reveals suspicions of counterfeiting; probable substitution of sulphacetamide to sulphadoxin. On the package, it is mentioned “Exclusively for St. Michael Pharmaceutical Ltd Lagos Nigeria.

Brand Name	Active Substance/Strength	Manufacturer/ Distributor	Procurement Site/Date	Concerns
Metronidazole 0,2g	Metronidazole 200mg	illegible (labeling in Chinese language)	Ets.Yang Yang Rue Secteur1 zone commerciale Ouagadougou January 31, 2010	The seller gave and could not write Metronidazole on the receipt.
Piroxicam 20mg	Piroxicam 20mg	Sine China	Hawker on the Patrice Lumumba road	The seller is illiterate and sells medicines labeled in Chinese language.

Annex 4: Samples collected in Ghana: February 19th to February 28th, 2010

Compare to other countries in the region, it is very rare to meet hawkers or peddlers along the roads in the cities. Substandard and illicit drug stores are localized in Agbogboloshi market, Nima market and Makola lorry station. Here, you may get your medicines only when you ask. Medicines are not exposed on market stalls. In drug stores and ordinary pharmacies medicines are sold even retailed in two capsules/tablets in small paper or nylon bags; according to your budget. No therapeutic plan is handed to patients. In many drugstores, vendors are illiterates or with very low education level.

Brand Name	Active Substance/ Strength	Manufacturer/ Distributor	Procurement Site/Date	Concerns
Amoxicillin 500mg	Amoxicillin 500mg	LetapPharmaceuticals Ltd	Healthmatch Pharmacy.Samora Marchel road Accra February 26, 2010	Medicines are sold without user information
Ampicillin 250mg	Ampicillin 250mg	Ayrton Drug Ltd. Accra	Licensed chemical Store Nima Accra	Medicines are retailed in small nylon bag .No user information available
Ampicillin Caps	Ampicillin 500mg	Letap Pharmaceuticals Ltd	Maple Leaf chemistry/Accra February 25, 2010	Medicines are retailed in small nylon bag .No user information available

Chloramphenicol Capsules	Chloramphenicol 250mg	Ayrton Drugs Ltd. Accra	Maple Leaf chemistry/ February 25, 2010	Sold in blister form without without user information attached.
Doxycycline Capsules 100mg	Doxycycline 100mg	Letap Pharmaceutical Accra	Ghana Postal Clinic February 25, 2010	Sold in blister form without user information attached.
Rocaf® Blister	Chloramphenicol 250mg	Ernest Chemistry Accra	Healthmatch Pharmacy.Samora Marchel road Accra February 26, 2010	Sold in blister unit without user information attached

Annex 5. Samples collected in Benin**:** March 2nd to March 6th, 2010.

Brand Name	Active Substance/ Strength	Manufacturer/ Distributor	Procurement Site/Date	Concerns
Ciplox 500®	Ciprofloxacin USP 500mg	CIPLA LTD India	Pharmacie des 4 Thérapies, Cotonou	No address from manufacturer/Distributor
Ery500mg® Batch:647	Erythromycin 500mg	Sophartex 28500Vernouillet France	Dantokpa Market, Cotonou. March 3, 2010	Ery 500mg was bought to compare the quality of the same product purchased from open market and from formal air conditioned pharmacy
Ery500mg® Batch:659	Erythromycin 500mg	Sophartex 28500Vernouillet France	Dantokpa Market, Cotonou. March 3, 2010	Ery 500mg was bought to compare the quality of the same product purchased from open market and from air conditioned pharmacy

Brand Name	Active Substance/ Strength	Manufacturer/ Distributor	Procurement Site/Date	Concerns
Ciplox 500®	Ciprofloxacin USP 500mg	CIPLA LTD India	Pharmacie des 4 Thérapies, Cotonou	No address from manufacturer/Distributor
Doxycycline 100mg	Doxycycline 100mg	KINAPHARMA LIMITED. North Industrial Area, Accra (Ghana)	Dantokpa Market, Cotonou. March 2, 2010	Blister has a name Doxykin; Mistake in dosage form/strength. Doxycyclingélules PB 100mg instead of BP 100mg

Annex 6: Samples collected in Togo: March 6th to March16th, 2010.

Official sources confirm that the pharmaceutical sector suffers from insufficiency of medicine professionals; one pharmacist for 300 patients according to the ministry of health. This situation should not be an excuse for turning a blind eye to the illicit medicine markets. Medicine sellers expose their goods on market stalls under inadequate storage conditions (high temperature). The itinerant hawkers are frequently met on streets even on the compounds of ministries. The sellers ignore that high temperatures may damage the potency of medicines they are carrying.

Brand Name	Active Substance/ Strength	Manufacturer/ Distributor	Procurement Site/Date	Concerns
Amoxicillin 500mg	Amoxicillin 500mg	Letap Pharmaceuticals Ltd. PO.BOX 3346, Accra	Assiganme Market Third Floor./ March 9, 2010	No package leaflet; that means no instructions for patients.
Cipox500®	Ciprofloxacin 500mg	ZIM Laboratories Ltd. B-21/22 MIDC Kalmeshwar Nagpur 441501 India	Assiganme Market, Lome (Togo). / March 9, 2010.	Inadequate package leaflet (repetition of composition

Cipro® 500mg USP	Ciprofloxacin 500mg	ZMC Hamburg GmbH, Germany.	Assiganme Market Third Floor./ March 9, 2010	The package leaflet is written with mistakes example Dosage form: Ciprofloxacin.
Cipromax® fort 500	Ciprofloxacin Hcl 500mg USP	Greenfield Pharmaceutical (Jiang Su) China	Assiganme Market./ March 9, 2010.	Information on packaging leaflet is not legible, leaflet too small. Concerns on readability.
RGI Doxycycline 100mg®	Doxycycline 100mg	Richy Gold International Ltd	Assiganme Market./ March 9, 2010.	It was mentioned on the package: Indication: Please refer to the leaflet although there was no leaflet in the package. "Store in a cool, dry and dark place" was translated "*Entreposer dans une place fraiche et sèche*". This is not the correct translation.
Shalcip500 ®:	Ciproflaxacin500g USP	Shalina Laboratories PVT Ltd., Mubai (India).	Assiganme Market/. March 9, 2010	The generic name Ciprofloxacin does not include the strength (500mg). The labeling of the storage conditions was not adequate.
Tetra250®	Tetracycline HCl 250mg	Sprukfield (UK) SARL BP. 1218 Lome Togo	Assiganme Market./ March 9, 2010.	No packaging leaflet attached. On the blister no instructions concerning side effect, dosage is not specified (as directed by the physician), no indication is mentioned.

9.2. Appendixes:

Appendix 1:

Itinerant Hawker in Abidjan's Streets

Appendix 2:

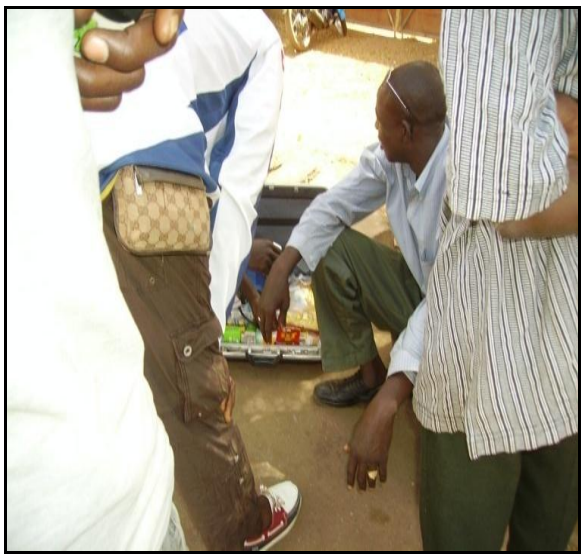
Illegal Drug Store in Lomé (Togo)

Appendix 3:

Medicines from a Hawker in Abidjan's (Cote d'Ivoire) Streets

Appendix4:

Medicines exposed to the sun
(high temperatures) for sale in the market



Appendix 5 & Appendix 6:

Illicit medicine marketing scenario in Ouagadougou (Burkina Faso)

Appendix 7:

Street Pharmacy in Cotonou (Benin)

Appendix 8:

Street Market for Medicines in Lomé (Togo)

Appendix 9:

Street Market for Medicines

in Lomé (Togo)

Appendix 10:

Market Stall of Medicines; Scenario in

Sub-Saharan Africa

Appendix 11:

Illegal stocking of medicines; but the administration closed such a drug store just for the non-payment of taxes; it means they close eyes to the legality aspect of such transactions

Appendix 12:

If the administration closed such a drug store just for the non-payment of taxes, it would mean that they close eyes to the legality aspect of such transactions

9.3. Figures and Tables

ServanTech GmbH & Co. KG, Dieselstr. 18, 61191 Rosbachv.d.Höhe April 2010

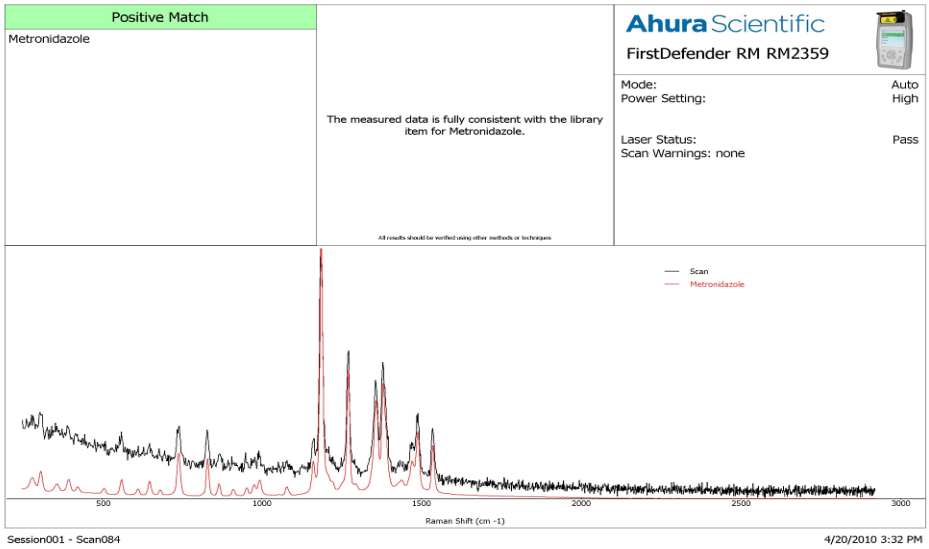


Fig 8: Raman spectrum of Metronidazole tablet (black) and pure API (red)

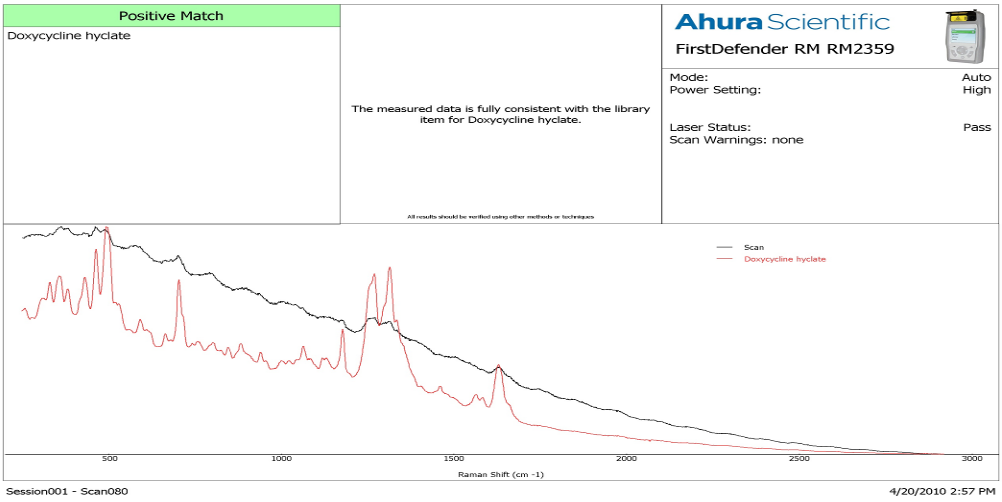


Fig 9*:* Raman application to Doxycap(Doxycycline) : API (red) identified in the product spectrum (Blue).Fluorescence present, but enough Raman signal to evaluate the sample.

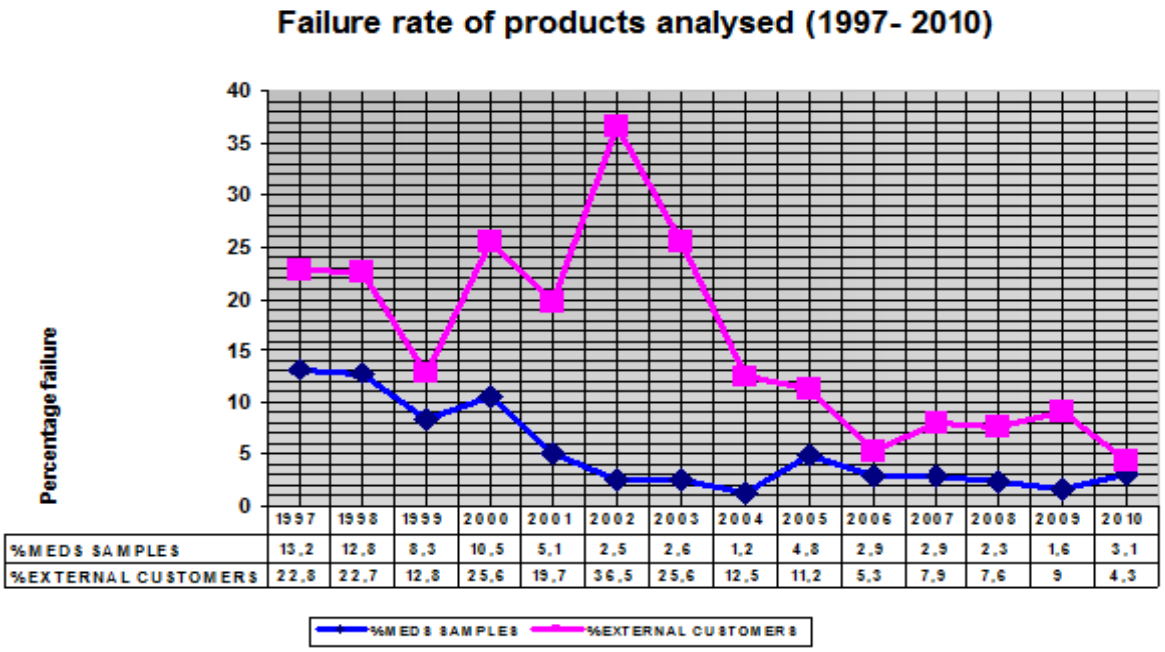


Figure 10: Implication of Prequalification: Failure rate of product analyzed 1997-2010

Source: Mission for Essential Drugs and Supply. Available from www.meds.or.ke.Internet accessed on March 7th, 2011

Table 11: Results from GPHF Minilab and visual inspection

Products/ procurement place	Manufacturer/ batch number	Visual test	Coloration	Disintegration	Thin layer chromatography
Cipromed® 500mg (Togo)	Medrel Pharmaceutical(India) PVP / S91198	No manufacturing site address; no company; no distributor references	Test not done due to shortage of time	The tablet disintegrates in water at 37° within 30 minutes	The result indicates the presence of ciprofloxacin
Ciproxamed® 500mg (Côte d´Ivoire)	Medrel Pharmaceutical (India) PVT /CPS805	No manufacturing site address; no company; no distributor references	Test not done due to allocated time	The tablet disintegrates in water at 37° within 30 minutes	The result indicates the presence of ciprofloxacin

Maloxin® (Sulfadoxin USP500mg+Pyrimethamine USP25mg (Burkina Faso)	ShreeChem Research Laboratories (India) EM 396 NAFDAC.04-1611	Blister is very hard to rip; the packaging leaflet contains no excipients	Poor coloration Yellow	Major defect; after 60minutes, not disintegrate	No remarkable spot under UV 254
Maloxin® (Sulfadoxin USP500mg+Pyrimethamine USP25mg (Nigeria)	Gracure Pharmaceutical (India) Nr. TE 2445	Blister is easy to rip.; the packaging leaflet contains information on excipients	Intensive yellow compared to batch from SchreeChem Laboratories. Less orange compared to the reference drug	Has passed disintegration within 30minutes	Remarkable spot at the same level for the reference drug
Shalcip 500mg®	Shalina Laboratories (India) Nr: MHDRUGS/PD 189	Abbreviation on the packaging leaflet: ENT / ORL were not explained.	Test not done due to allocated time	The tablet disintegrates in water at 37° within 30 minutes	The result indicates the presence of ciprofloxacin
Tetra 250mg® (Togo)	Togo Sprukfield (UK) GMbH/AV09003	No packaging leaflet	More intense colour compared to the reference drug	Test not done due to allocated time	Test not done due to allocated time

Table 12: Some parameters of medicines market in survey countries (data from countries reports)

Country	Date of Visit	Population in Million (2007)	Per capita total expenditure on health at average exchange rate (US$.2006)	Out of pocket expenditure as % of total expenditure on health	Life expectance at birth (2007)	Pharmacists	Manufacturers	Distributors	Retail outlets (Shops are outlets not under supervision of pharmacist)
Benin	February 2010	9.033	$26	$47	57	235	2	5	245 shops
Burkina Faso	January 2010	14.784	$27	$39	49	245	5(including .traditional medicines)	6	155
Cote d´ivoire	February 2010	19.262	$35	$67	54	933	8(including . inactives)	3	No data available
Ghana	February 2010	23.478	$33	$51	57	1798	29	no data	1186 operated by pharmacist, 9814 licensed outlet
Nigeria	January 2010	148.093	$33	$64	49	6748 [29]	132 (approx. 60 registered	995	1604,and undetermined shops
Togo	March 2010	6.48	$ 19	$45	55	230	2	4	No, data available

Sources: WHO. World Health Statistics 2009, and Data from countries survey

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Curriculum Vitae

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2009-2012

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Ndjamawe Bah-Traore, Ludwig Hoellein, Johannes Baeumert, Harald G Schweim, Ulrike Holzgrabe, Poor manufacturing practices and the problem of substandard medicines in sub-Saharan Africa, Regulatory Affairs Journal Pharma Online-Version November 2011, printed Version November 2011, Page 18 -20.

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