THE UNIVERSITY OF ZAMBIA

SCHOOL OF MEDICINE

DEPARTMENT OF PUBLIC HEALTH

QUALITY ANALYSIS OF SELECTED PEDIATRIC HIV/AIDS/TB MEDICINES IN LIVINGSTONE DISTRICT, SOUTHERN PROVINCE, ZAMBIA.

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A dissertation submitted to the University of Zambia in partial fulfillment of the requirements of the degree of Master of Public health in Health policy and management.

The University of Zambia

Lusaka

2013

DECLARATION

I hereby declare that this dissertation represents my own work and has not been presented either wholly or in part for a degree at the University of Zambia or at any other University.

Signed……..
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I have read this dissertation and recommend it for examination

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DEDICATION

Many thanks to my wife Angela N Chigunta, my daughter Jane L Chigunta and son Solomon M Chigunta for having being there for me all the way, May the good Lord continue blessing you.

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ACKNOWLEDGEMENTS

It is my duty and responsibility to thank all people who contributed in my training and the outcome of this research.

The Management and all authorities of the School of Medicine, University of Zambia.

My ever good Supervisor, DR S.H Nzala, continue the good work and may God richly bless you and your family.

The Head of the Department of Public Health, Dr Charles Michelo for ensuring that work was correctly done on time.

The Ministry of Health of the Republic Zambia, for being there for me and partially sponsoring my school work.

The Leadership of PRA and more especially,MrBornaventureChilinde, the Quality Control Manager for his dedication.

All my class mates that formed the first class of the Health Policy and Management specialty, it was really a good experience to share the same class with you guys, my God bless our future endeavors.

ABSTRACT

Introduction

Counterfeiting affects all medical products, from medicines and pharmaceutical ingredients to medical devices and diagnostics. Counterfeit drugs including overt forgeries, pharmaceutically-sound close imitations, substandard generic medications, gray pharmaceuticals, and repackaged expired drugs are not only a problem of the developing world. It is therefore important to know or ascertain the quality of medicines or drugs being consumed by the population for public health protection. This study was designed to evaluate the quality of selected pediatric HIV/AIDS and TB drugs in Livingstone district health facilities of Zambia.

Methodology

The study was a cross sectional study that involved the collection of samples of different brands/lots of pediatric Nevirapine (NVP) suspension as well as Rifampicin-Isoniazid (RH) tablets in Livingstone District health facilities. A total of 400 RH tablets and 50 bottles of NVP suspension of different brands and batches were collected, kept and transported to Lusaka for analysis at ambient temperature. The analysis involved assessing for presence of Active Pharmaceutical Ingredients, percentage content, packaging, appearance and labeling standards with reference to the official monographs in this case the International Pharmacopoeia 2011 (IP) and the United State Pharmacopeia 36 (USP).

Results

A total of 450 drug samples were included in the study and 100% were correctly identified, had the active pharmaceutical ingredient in the right quantities, appeared, labeled and packaged in conformity with the official monographs of the USP 36 and IP 2011.

Conclusion

This study provided objective evidence that the selected pediatric medicines available in Livingstone District Health facilities of the Republic of Zambia are of good quality and meet the requirements as stipulated in the official monographs of the USP and IP.

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ABBREVIATIONS

ADR – Adverse Drug reaction

AIDS – Acquired Immune Deficiency Syndrome

API – Active Pharmaceutical Ingredient

ARV – Antiretroviral

AZT – Zidovudine (Azidothymidine)

BP – British Pharmacopoeia

CSO – Central Statistical Office

D4T - Stavudine

ERES – Excellence in Research Ethics and science

FDC – Fixed Dose Combination

FIP – International Pharmaceutical Federation

GMP – Good Manufacturing Practice

HAART – Highly Active Antiretroviral Therapy

HIV – Human Immunodeficiency Virus

IFPMA- International Federation of Pharmaceutical Manufacturers Association

IMPACT - International Medical Products Anti-Counterfeiting Taskforce.

IP- International Pharmacopoiea

MDG – Millennium Development Goals

MOH – Ministry of Health

NAC – National AIDS Council

NVP–Nevirapine

PMTCT – Prevention of Mother To Child Transmission of HIV/AIDS

PRA – Pharmaceutical Regulatory Authority

RH – Rifampicin/ Isoniazid

TB - Tuberculosis

TLC – Thin Layer Chromatography

UNZA – University Of Zambia

USP – United States Pharmacopoeia

WHO – World Health Organization

ZDHS – Zambia Demographic and Health Survey

OPERATIONAL DEFINITIONS

Active pharmaceutical ingredient – the drug substance of a pharmaceutical product purported to have therapeutic activity

Analysis - the identification or separation of ingredients of a substance or carefully examining something in order to understand it better.

Antiretroviral drug- medicine used in the management of HIV/AIDS

Batch number- a serial code depicting products/ goods produced in one operation.

Counterfeit medicine/drug- are any brand (or generic) medicines and active pharmaceutical ingredients (APIs) that are deliberately and fraudulently mislabeled by unauthorized parties with respect to source, and / or composition and / or therapeutic quality.

Fake medicine - one that is not what it purports to be or a worthless imitation passed off as genuine.

HIV/AIDS- refers to a disease condition that weakens the human body's immune system leaving it susceptible to various illnesses resulting from a viral infection known as the Human Immune Deficiency Virus.

Medicine/drug- any chemical substance used in the prevention, diagnosis, cure, mitigation and treatment of disease or that which may be used for the modification of the normal physiological body functions.

Official monograph- all pharmaceutical standard reference books such the British pharmacopeia and the United States Pharmacopoeia

Quality – the degree of excellence and orthe character in a logical proposition of being affirmative or negative

Substandard drug- a drug with genuine packaging but with incorrect quality of ingredients or different or absence of active pharmaceutical ingredient as stated on the label

Thin layer chromatography- a laboratory analytical method used for dug analysis

Tuberculosis- a bacterial infection caused by the organism Mycobacterium Tuberculae.

CHAPTER 1
1.0 INTRODUCTION

Counterfeiting affects all medical products, from medicines and pharmaceutical ingredients to medical devices and diagnostics. The terms "counterfeit drugs" and "substandard drugs" are often confused. For public health purposes, the World Health Organization (WHO) defines a counterfeit drug as one that is "deliberately and fraudulently mislabeled with respect to identity and/or source," and substandard drugs as, "genuine drug products which do not meet quality specifications set for them."(WHO/IMPACT, 2006)If substandard drugs are knowingly produced to make an unlawful product, they too are considered counterfeit. Furthermore, an additional "gray pharmaceutical" space is emerging where illicit profiteers are ostensibly marketing competitive brands without regulatory approval. These products are seldom "counterfeit" *per se*, but are very often substandard. Nonetheless, they threaten virtually all of the negative consequences of a *bona fide* WHO-defined counterfeit: circumvention of health regulations, undercutting public confidence, and potentially providing a comparatively easy source of income to criminal elements (WHO, 2006). Because this is an opportunistic crime, the United Nations Office for Drugs and Crime (UNODC) finds that this type of counterfeiting is more likely to emerge where regulatory capacity is low (UNODC, 2012). Surveys of anti-infective medications in Asia and Africa, for instance, have found as much as 60 percent of local drug supplies with active ingredients outside of medicinal limits. In West Africa, anti-malarial medicine, antibiotics, anti-tuberculosis drugs, and anti-retrovirals have all been targeted by counterfeiters resident most especially in South and East Asia.Counterfeiting is greatest in those regions where the regulatory and legal oversight is weakest(WHO, 2008). Most industrialized countries with effective regulatory systems and market control (e.g. USA, most of EU, Australia, Canada, Japan, and New Zealand) have an extremely low proportion of counterfeit drugs, i.e. less than 1% of market value (WHO, 2006).

In responding to the growing global public health crisis of counterfeit drugs, the WHOin February 2006, launched the International Medical Products Anti-Counterfeiting Taskforce (IMPACT). At its core, IMPACT aims to build coordinated networks across and between countries in order to halt the production, trading and selling of fake medicines around the globe. IMPACT is a partnership comprised of all the major anti-counterfeiting players, including: international organizations, non-governmental organizations, enforcement agencies,

pharmaceutical manufacturers associations and drug and regulatory authorities (WHO/IMPACT, 2006).

As indicated by the data presented above, it is important to note that counterfeit drugs including overt forgeries, pharmaceutically-sound close imitations, substandard generic medications, gray pharmaceuticals, and repackaged expired drugs are not only a problem of the developing world. A growing volume of interdictions in the industrialized world shows that counterfeits are also pursuing Western markets. In many countries, including many across the developed world, weak or insufficient enforcement has contributed to these steadily rising trends. Drug regulatory systems in most countries, including in North America, expend far more time and effort on pre-marketing approvals than on post-market monitoring (WHO, 2006). No matter how thoroughly premarketing assessment is conducted, it is only one of the functions necessary for ensuring the efficacy and safety of drugs. Indeed, a recent WHO study found that less than 20 percent of the organization's member states are thought to have a well-developed drug regulation system (WHO, 2006).

The International Pharmaceutical Federation (FIP) and International Federation of Pharmaceutical Manufacturers Association (IFPMA) have a common goal to protect the well-being of patients in all parts of the world by ensuring that all medicinal products are of good quality and proven safety and efficacy (FIP, 2003). Both industry and the pharmaceutical profession recognize the need for a regulatory and marketing environment which encourages investment in new innovative medicines and allows their timely introduction and availability to patients world-wide. FIP and IFPMA give priority to the need for effective regulatory safeguards to ensure that the patient is protected from the hazard to health of poor quality, substandard and counterfeit medicines (FIP, 2003).

Governments, including the Republic of Zambia, have an obligation to protect their citizens and therefore must ensure that medicinal products, whether manufactured locally or imported, meet recognized international standards of quality, safety, bioavailability and efficacy. The same principles for standards must be applied by Governments for both branded and generic products and for both the private and public sectors. Achievement of high standards depends upon a combination of the commitment of manufacturers to Good Manufacturing Practice (GMP),

satisfactory legislation, effective and comprehensive regulatory procedures and effective inspection and enforcement arrangements, together with the political will to implement them (WHO, 2006).

According to the WHO, children with TB represent 10 % to 20 % of all TB cases. The majority of these cases occur in low-income countries where the prevalence of Human Immunodeficiency Virus/ Acquired Immunodeficiency Syndrome (HIV/AIDS) is high (WHO, 2012). At the global level, the importance of tuberculosis and its association with HIV/AIDS pandemic are acknowledged by the Millennium Development Goals (MDGs), and unprecedented amounts of funds are being provided by the Global Fund to combat HIV/AIDS, Tuberculosis and Malaria (WHO, 2006). Zambia has joined the rest of the world in striving to attain the MDGs in response to the world's main development challenges. MDGs number 4 and 6 are of interest in this study as they address issues of child mortality and HIV/AIDS, Tuberculosis and other infectious diseases. Combating the above mentioned communicable diseases will require the use of quality, safe and efficacious drugs. To this effect, the Republic of Zambia established the Pharmaceutical Regulatory Authority in 2004 whose main functions, among others, are to provide for the registration and regulation of medicines intended for human use and for animal use; to provide for the regulation and control of medicines, herbal medicines and allied substances; to provide for the regulation and control of the manufacture, importation, exportation, possession, storage, distribution, supply, promotion, sale and use of medicines, herbal medicines and allied substances (Pharmaceutical Act, 2004).

Counterfeiters take inert ingredients such as chalk, and even dangerous chemicals, package them convincingly and sell them to consumers according to Burns (2006). Such drugs may have no therapeutic effect and can be toxic. If drugs contain too little of the active ingredients, not all of the disease agents are killed and resistant strains are able to multiply and spread. More importantly, substandard medicines typically provide inadequate doses of drugs, either because too little active ingredient is included in tablets or because the delivery vehicles are inappropriate. Consumers or patients of such medicines may die or get far sicker than would have been the case if they had received an adequate dose according to Kalesidis et al (2007).

1.1 HEALTH AND ECONOMIC IMPACT

Counterfeit, sub-standard as well as fake medicine presents a major obstacle to the treatment of deadly diseases, including malaria, tuberculosis, and HIV/AIDS in sub-Saharan Africa. The widespread awareness of these drugs and troubling victimization especially in poor countries add to a long list of health and wellbeing challenges in the region.

Perhaps one of the most worrying implications of the global boom in substandard medicines is the acceleration of new, drug resistant strains of viruses, parasites and bacteria which in the long run may result in huge treatment costs for individual patients as well as countries or governments (WHO, 2007).

Counterfeit pharmaceuticals in Africa indicate a wide variety of detrimental effects. In addition to those in public health, these include lost revenues to firms that might otherwise be used to develop newer and better products, lost taxes to governments responsible for public health, additional costs firms and governments incur to protect supply chains from counterfeit products, resulting in disincentives to foreign investment, and consequent loss of jobs and economic opportunities (WHO, 2008).

1.2 STATEMENT OF THE PROBLEM

In order to mobilize awareness and action in the fight against counterfeit, substandard and fake drugs, WHO in February 2006, created the first global initiative known as IMPACT. IMPACT is comprised of all 193 WHO Member States on a voluntary basis and includes international organizations, enforcement agencies, national drug regulatory authorities, customs and police organizations, nongovernmental organizations, associations representing pharmaceutical manufacturers and wholesalers, health professionals and patients' groups. These groups have joined to improve coordination and harmonization across and between countries so that eventually the production, trading and selling of these medicines will cease.

For almost 30 years now, WHO has been fighting drug counterfeiting since it became a major threat in the 1980s. The problem was first noticed by the pharmaceutical industry which saw that their own products were being copied.

WHO estimates that 8% to 10% of the medicines in the global medicine supply chain are counterfeit, reaching as high as 25% in some countries. An estimated 1 in 4 packets of medicine sold in street markets in developing countries could be substandard (WHO, 2006).

Although it is difficult to obtain precise figures for substandard drugs, the Food and Drug Administration (FDA) in the United States of America estimates that worldwide sales of fake drugs exceed US$ 3.5 billion per year (FDA, 2005). The Center for Medicines in the Public Interest in the USA predicted that counterfeit drug sales could reach US$ 75 billion globally in 2010 if action was not taken to curb the trade (WHO, 2006).

According to WHO, drugs commonly counterfeited include antibiotics, antimalarials, hormones and steroids, while increasingly, anticancer and antiretroviral drugs are also faked. Counterfeit drugs are found everywhere, but sub-Saharan Africa is particularly affected. In Africa, drugs are sold through the informal economy in large open-air markets alongside fruits and vegetables (WHO, 2006).

A recent study on the quality of anti-malarial in sub-Saharan Africa conducted by the WHO revealed a high failure rate. The study found that 44% of samples from Senegal and 30% from Madagascar could be qualified as of inferior quality (WHO, 2011).

In studies assessing the quality of anti-malarials (chloroquine and sulfadoxine / pyrimethamine) in Yemen, the results indicated high and low failures in ingredient content for chloroquine tablets and chloroquine syrup respectively. It was feared these medicaments could have reduced therapeutic effectiveness and lead to the development of drug resistance (Ahmed, 2005).

Unfortunately, the exact extent of this problem, and therefore how best to combat it, is unknown, but according to WHO, factors that have been suggested to contribute to the production of substandard drugs in especially developing countries including Zambia are: lack of political will and commitment to fight the scourge, weak legislation prohibiting counterfeiting of drugs, absence of or weak national drug regulatory authorities, weak drug laws enforcement and penal sanctions, shortage or erratic supply of drugs, high cost of medicines, ineffective cooperation among stakeholders, trade involving several intermediaries, inadequate skilled human resource to run the system and corruption and conflict of interest (WHO, 2006). However, the key areas to focus on to combat the global scourge include but are not limited to:

- Legislative and regulatory infrastructure development.
- Regulatory implementation.
- Regulatory enforcement.
- Technology development.
- Communication with all stakeholders.

In Zambia, however, the problem is further compounded by the Pharmaceutical Regulatory Authority being centralized, making it difficult for the institution to run their welfare.

According to WHO, out of the 193 WHO member states, only about 20% are known to have well-developed medicines regulation and enforcement. 50% of the member states implement regulation at various levels and 30% have no medicines regulation in place or only very limited capacity that is hardly enforced (WHO, 2012).

1.3 STUDY JUSTIFICATION

As a global public health crisis, counterfeit medicines represent anenormous public health challenge. Even one single case of counterfeit medicine is not acceptable because,in addition to putting patients at riskand undermining the public confidencein their medicines, it also betraysthe vulnerability of the pharmaceuticalsupply system and jeopardizes thecredibility of national authorities(WHO, 2008).There is no documented evidence in terms of research with regard to the existence of counterfeit pediatrics ARVs and TB drugs on the Zambian market. However, some work has been done in developed countries, within the region and Zambia on other drugs such as anti-malarialsand adult anti-TB drugs, which show that counterfeits are present ranging from about 5% to 38%.

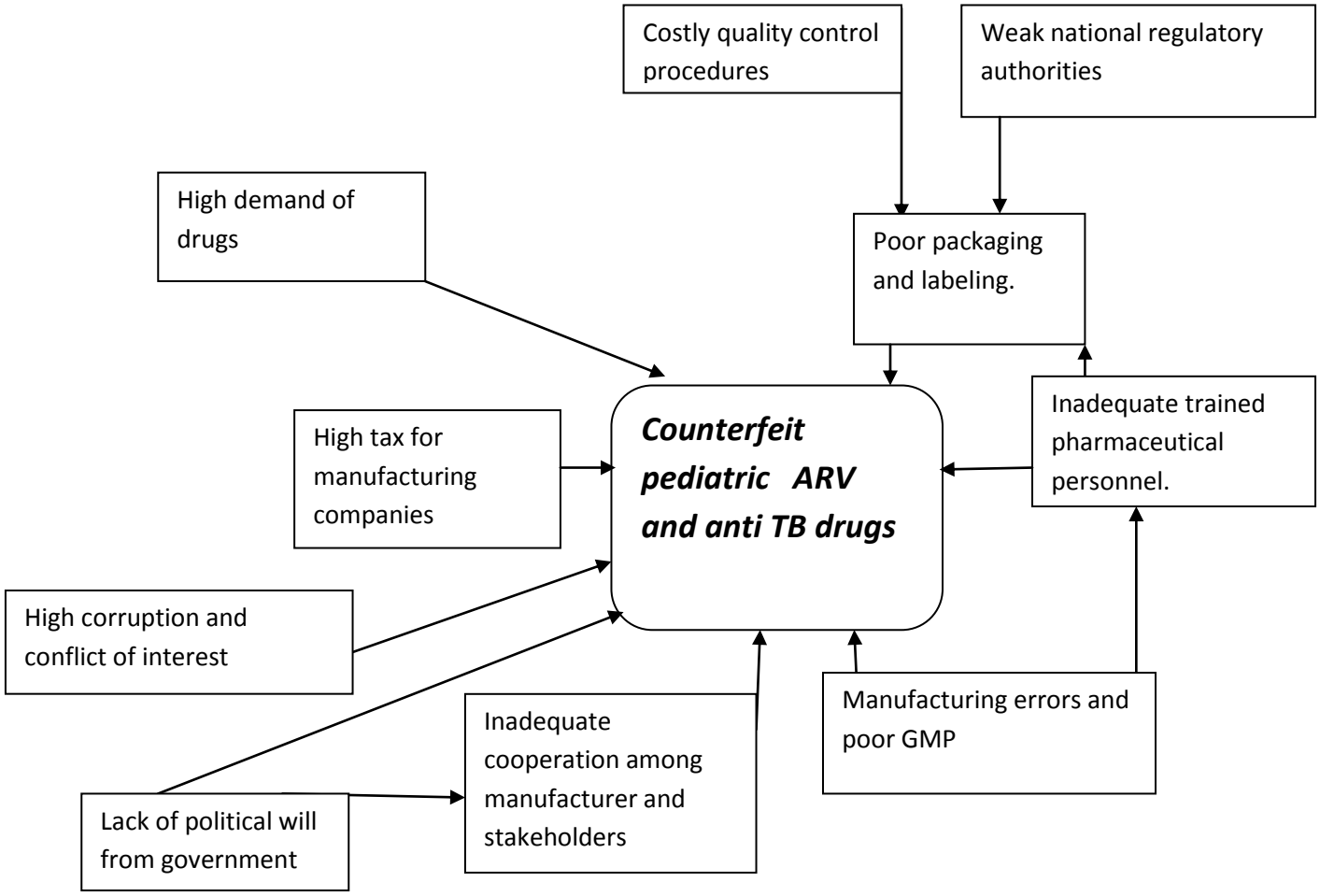
The drugs involved in this study are pediatrics Rifampicin-Isoniazid and Nevirapine suspension. There has been an increase in the relapse cases of TB as well as Multi Drug Resistance TB (MDR) cases in Livingstone District and the Country at large. Among other factors thought to affect this problem is the poor quality of drugs which almost always are in short supply and rushed to service delivery points upon receipt, sometimes even before Quality Control tests are done by the National Drug Quality Control Laboratory at PRA. The resistance of TB to Rifampicin and Isoniazid is what is termed as MDR TB.

The Prevention of Mother To Child Transmission (PMTCT) of HIV/AIDS, National Protocol for all children born to HIV/AIDS positive mothers are commenced on Nevirapine suspension until after a week after breast feeding or as determined by the health care specialist looking after the child. The drugs chosen in this study play a key role in Zambia as the country tries to attain the Millennium Development Goals especially MDG number four (4) and six (6).

This study therefore, aimed at evaluating the quality of selected pediatric HIV/AIDS and TB drugs in Livingstone district. Recommendations pertaining the quality of selected pediatric ARVs and Anti TB drugs in Livingstone District have been made to PRA and MOH as this study may help in policy formulation and implementation. This report may help find ways of strengthening the fight against counterfeiters as well as the emergence of drug resistance which is another major result of counterfeiting. It is also hoped that some information therein, may help maximize the effectiveness of the pediatric ART and TB programs.

1.4 PROBLEM ANALYSIS DIAGRAM:

Problematic issues related to counterfeit drugs



1.5 Research Questions

1. Does the quality of available pediatric ARVs and Anti TB drugs in health institutions of Livingstone District meet the set standards as prescribed in the official monographs?

1.6 General Objective

To determine the quality of selected pediatric ARVs and anti TB drugs available in health facilities of Livingstone District.

1.7 Specific Objectives

i. To verify the active ingredients contained in samples ofNevirapine (NVP) suspension and Rifampicin-Isoniazid (RH) tablets
ii. To assess the packaging and labeling standards on the containers of NVP suspension and RH tablets.
iii. To determine the proportions of NVP suspension and RH tablets substandard in the drug samples.

CHAPTER 2

2.0 LITERATURE REVIEW

Currently, the sources of information available on counterfeit drugs include reports from nongovernmental organizations, pharmaceutical companies, national drug regulatory and enforcement authorities,ad hoc studies on specific geographical areas or therapeutic groups, and occasional surveys. These sources of information emphasize the complexity of making estimations. Although precise and detailed data on counterfeit medicines is difficult to obtain, IMPACT stakeholders estimate proportions ranging from around 1% of sales in developed countries to over 10% in developing countries, depending on the geographical area (WHO/IMPACT, 2006). That range takes into consideration both regional disparities in the presence of counterfeits, and specific global market value shares. Apart from the huge differences between regions, variations can also be dramatic within countries, i.e. city versus rural areas, city versus city. Counterfeiting is greatest in those regions where the regulatory and legal oversight is weakest. Most industrialized countries with effective regulatory systems and market control (e.g. USA, most of EU, Australia, Canada, Japan, New Zealand) have an extremely low proportion of counterfeit medicines, i.e. less than 1% of market value (WHO, 2006).

2.1 GLOBAL PERSPECTIVE

WHO estimates that 8% to 10% of the medicines in the global medicine supply chain are counterfeit, reaching as high as 25% in some countries (WHO, 2011). The largest counterfeit market with close proximity to the EU is Russia, where it is estimated that 12% of medicines are counterfeit. Counterfeit medicines are entering Europe's legitimate supply chain in increasing numbers. More than 8.8 million counterfeit medicines packs were seized at Europe's borders in 2008, a 118% increase on the previous year (WHO, 2008). According WHO 2006, around one percent of medicines in Europe are now counterfeit.

The WHO has previously estimated that 200,000 deaths per annum would be preventable if drugs used were not fakes. They calculated this from statistics in two papers: the Africa Malaria Study 2003, and The Quality of antimalarials - A Study in Selected African Countries (WHO 2003). The calculations assumed that there were 1 million annual deaths from malaria, with only

half of these victims being diagnosed and receiving any treatment at all. Of these, a fifth were estimated to have been resistant to chloroquine and sulfadoxine-pyrimethamine, leaving 400,000 lives capable of being saved through treatment (given existing levels of coverage). The study asserted that, according to the research in The Quality of Antimalarials - A Study in Selected African Countries, up to half of antimalarial drugs in some areas was substandard, and therefore up to half the 400,000 preventable deaths were due to substandard products. This figure may be conservative. Since then artemisinin use has become far more widespread, meaning that the 100,000 deaths removed from the equation now arguably should not be. This, by their methodology, would increase their figure to 250,000 deaths. In parts of Asia fake antimalarials account for as much as 68% of the market, and drug resistant malaria is growing as a consequence. Fakes are at the very least partially culpable for deaths from drug resistant disease (WHO, 2003).

After the marketing of the artemisinin-based combination therapy (ACT) against malaria in Asia, these costly drugs were found to be counterfeit in 38% and 53% in two studies conducted in different countries of south-east Asia. In Cambodia, for example, it was shown that fake artesunate was sold by 71% of local drug vendors according to Ahmed, Bassili and Atta (2005).

According to the WHO, there were 9.3m new cases of TB in 2007. Coverage of Directly Observed Treatment (DOTs) is said to be around 94% worldwide, with half of untreated sufferers expected to die. Data on levels of fake TB drugs is scarce, yet one reliable study (Laserson et al, 2001) across six countries found the level to be 10%. This leaves approximately 900, 000 people suffering from TB and receiving treatment with fake drugs. The chances of dying from TB if not treated correctly are 50%, so we can assume this situation could lead to approximately 450,000 deaths.

The United States Food and Drug Administration (FDA) issued an alert about a counterfeit antiretroviral medicine (FDA, 2007).The Dutch Healthcare Inspectorate warned consumers not to buy Oseltamivir, a flu medication, through the Internet, after counterfeit capsules were found in the Netherlands containing lactose and vitamin C, and no active substance while in the same year in the United Kingdom, officials seized 5000 packets of counterfeit flu medication Oseltamivir (WHO/IMPACT, 2006).These examples clearly highlight how rampant this problem has escalated that if not taken seriously may lead to negative health and economic effects.

Globally, it is estimated that more than US$ 30 billion per year are earned by the overall trade of substandard and counterfeit drugs and this will probably increase to over US$ 75 billion by the year 2012.

2.2 REGIONAL PERSPECTIVE

A study by the International Policy Network (IPN) reveals the shocking burden of fake medicines in the sub-saharan region. Fake tuberculosis and malaria drugs alone are estimated to kill 700,000 people a year (IPN, 2009).The report lays bare the ballooning problem of counterfeit and substandard drugs, which can constitute one third of the drug supply in certain African countries. These dodgy drugs result in unnecessary death and increased levels of drug resistance. The report highlights more shocking evidence, such as:

- Nearly half the drugs sold in Angola, Burundi, and the Congo are substandard.
- About two thirds of artesunate (anti-malarial) drugs in Laos, Myanmar Cambodia and Vietnam contain insufficient active ingredient.
- Most fake drugs originate from China and India

Gallup surveys conducted in 2010 show counterfeit drugs are widespread in sub-Saharan Africa, where these drugs are often used to treat malaria, tuberculosis, and HIV/AIDS. Majorities in 15 of 17 countries Gallup polled in sub-Saharan Africa say they are aware of fake medicines in their countries. Researchers in Lagos, Nigeria tested 13 brands of Artesunate-Amodiaquine combinations bought from local pharmacies and found 85 percent failed to meet USP specifications for one of the active ingredients (Taylor, 2012). The results add to the concern about substandard drugs in sub Sahara Africa.

2.3 NATIONAL PERSPECTIVE

According to the Post news papers Zambia, The PRA says "counterfeit products have become a very serious matter in Zambia, outlining that the authority's biggest challenge is people operating illegal drug stores in the country" (Nkonde, 2012, p. 4).

According to a study by the Alliance for the Prudent Use of Antibiotics (APUA), Indian manufactured drugs account for about 58% of those found on the Lusaka market while Locally manufactured drugs account for only a small percentage of available drugs, approximately 4%, The origin/source could not be determined in 38% of samples, mostly those sold from large containers of 100 and 1000 tablets. They mentioned that one potential driver of antibiotic resistance could be poor drug quality and that drug quality effort should focus on other drugs such as antimalarials and antiretroviral (APUA, 2011). Some work has been done on other drugs such as Co-trimoxazole tablets (Zyambo, 2008) and adult Fixed Dose Tuberculosis medicines (Mweemba, 2011)which show that counterfeits are present with results ranging from about 5% to 20%, while another study by Munkombwe (2011) did not find any adult ARVs under review to be counterfeit.

It is realized that counterfeit medicines;

- Have harmful effects on patients health and can kill;
- Frustrate efforts to deal with high burden of disease;
- Undermine the credibility of the health care system and therefore;
- Increased international collaboration is essential to beat the global scourge.

It must however be appreciated that the government of the Republic of Zambia has shown its commitment to fight this Global scourge of counterfeiting by the establishment of institutions such as the PRA.

CHAPTER 3

3.0 RESEARCH METHODOLOGY

3.1 Variables of the study

Independent variables

- Active ingredients
- Percentage content of active ingredients
- Packaging material
- Labeling information

Dependant variables

- Counterfeit (include Fake or Substandard drugs).

3.2 Study setting

The study was conducted in Zambia's tourist capital city, Livingstone, which is one of the towns with high levels of both HIV/AIDS and Tuberculosis. The drug samples were collected from four (4) main public health institutions offering pediatrics HIV/AIDS and Tuberculosis services within Livingstone District. These are Livingstone General Hospital, Maramba Urban Health Center, Libuyu Clinic and Mahatma Ghandi Urban Health Center. The analysis of the samples was done in Lusaka at PRA National Drug Quality Control laboratories.

3.3 Study samples

The study samples comprised of 50 bottles of NVP suspension,and 400 tablets of RH. These were randomly selected from the health facilities within Livingstone district taking into account the different brands and batch numbers so as to avoid duplication of the samples using a carefully designed data collection tool.

3.4 Study design

A cross sectional study was conducted using convenient sampling technique and 5 parameters were considered. These included

1. Appearance of the dosage form(e.g. tablets, suspension)

2. Labeling information
3. Type of packaging material
4. Presence of active ingredients in the samples
5. Percentage content of active ingredients as outlined in official monographs (BP and USP)

3.5 Inclusion criteria

Only pediatrics first line formulations of ARVs and anti TB drugs were included in the study, for as long as they were not expired with reference to the expiry date on the label and with at least 6 months before expiry date.

3.6Exclusion criteria

All the first line pediatrics ARVs and TB drugs with less than 3 months to expiry date as well as second line drugs were not included in the study.

3.7Sampling method

A systematic sampling method was used to select the health facilities while simple random sampling was used for the actual sample collections which werekept at ambient temperature until the analysis time which was at least four (4) weeks after collection.

3.8Sample size determination

The following formula has been employed to calculate the sample size for analysis;

$n = Z\ P\ (100 – P)/d$

Where; Z = 1.96, factor from normal distribution

P = Expected period prevalence

d = Absolute sampling error

n = Sample size

Therefore, n = (1.96) x 50 (100 – 50)/ 5 = 384 tablets and suspensions.(i.e. 390 tablets and 40 suspensions). Adjusting for handling loses set at 10% gives us 422 total sample sizes but was rounded off to 450.

3.9Data collection tool

A drug collection sheet, which provides information on the date, place, condition of the dosage forms, name of drug and active ingredient as indicated by the manufacturer on the packaging label, was used.

3.10Data collection

Drug samples were collected from four (4) main health facilities offering both pediatrics HIV/AIDS and TB services and were kept at ambient temperature until analysis.

3.11Data analysis

The samples were analyzed atPRA Laboratories using HPLC. Manual calculations and comparisons with official monographs weredone.

HPLC operation

HPLC is a chromatographic technique used to separate the components in a mixture, to identify each component, and to quantify each component. HPLC is considered an instrumental technique of analytical chemistry. In general, the method involves a liquid sample being passed over a solid adsorbent material packed into a column using a flow of liquid solvent. Each analyte in the sample interacts slightly differently with the adsorbent material, thus retarding the flow of the analytes. If the interaction is weak, the analytes flow off the column in a short amount of time, and if the interaction is strong, then the elution time is long. HPLC has been used in medical (e.g. detecting vitamin D levels in blood serum), legal (e.g. detecting performance enhancement drugs in urine), research (e.g. separating the components of a complex biological sample, or of similar synthetic chemicals from each other), and manufacturing (e.g. during the production process of pharmaceutical and biological products).

Chromatography can be described as a mass transfer process involving adsorption. HPLC relies on pumps to pass a pressurized liquid and a sample mixture through a column filled with a

sorbent, leading to the separation of the sample components. The active component of the column, the sorbent, is typically a granular material made of solid particles (e.g. silica, polymers, etc.), 2-50 micrometers in size. The components of the sample mixture are separated from each other due to their different degrees of interaction with the sorbent particles. The pressurized liquid is typically a mixture of solvents (e.g. water, acetonitrile and/or methanol) and is referred to as a "mobile phase". Its composition and temperature plays a major role in the separation process by influencing the interactions taking place between sample components and sorbent. These interactions are physical in nature, such as hydrophobic (dispersive), dipole-dipole and ionic, most often a combination thereof.

The schematic of an HPLC instrument typically includes a sampler, pumps, and a detector. The sampler brings the sample mixture into the mobile phase stream which carries it into the column. The pumps deliver the desired flow and composition of the mobile phase through the column. The detector generates a signal proportional to the amount of sample component emerging from the column, hence allowing for quantitative analysis of the sample components. A digital microprocessor and user software control the HPLC instrument and provide data analysis. Various detectors are in common use, such as UV/Vis, photodiode array (PDA) or based on mass spectrometry.

The sample mixture to be separated and analyzed is introduced, in a discrete small volume (typically microliters), into the stream of mobile phase percolating through the column. The components of the sample move through the column at different velocities, which are function of specific physical interactions with the sorbent (also called stationary phase). The velocity of each component depends on its chemical nature, on the nature of the stationary phase (column) and on the composition of the mobile phase. The time at which a specific analyte elutes (emerges from the column) is called its retention time. The retention time measured under particular conditions is considered an identifying characteristic of a given analyte.

3.12Data quality control checks

The researcher worked closely with the laboratory quality control manager at PRA so as to ensure that all protocols were followed as provided for in the official monographs.

3.13Ethical consideration

This study did not involve human participants directly.However, clearance was sought from the ERES CONVERGE IRB. Permission was sought from the Permanent Secretary of the ministry of health and other relevant authorities for sample collection from public health facilities offering both pediatric HIV/AIDS and TB services.

CHAPTER 4

4.0 RESULT

A total of 400 RH tablets and 50 NVP suspension sample bottles were collected from four public health facilities of Livingstone district. The samples were collected from Livingstone General Hospital, Maramba Urban Health Center,Libuyu health center and Mahatma Ghandi Health Center. Care was taken when sampling so as to ensure different brands and batches were collected.

The samples used in this study are anti-TB medicines used in the treatment of TB in children as well as NVP suspension, an anti HIV medicine used in both the treatment as well as prevention of HIV infection in children born to HIV positive mothers according to the national treatment guidelines for Zambia. The table below shows the samples used, drug class as well as the references used for analysis but does not show the actual batch numbers for ethical reasons.

Table 1, Samples and references used.

SAMPLE	**SAMPLE CODE**	**API**	**FORMULATION**	**REFERENCE MATERIAL USED**
R	1 (A,B and C)	Rifampicin	Tablets	International Pharmacopoeia 2011
H	2 (A,B and C)	Isoniazid	Tablets	International Pharmacopoeia 2011
NVP	3 (A,B and C)	Nevirapine	Suspension	United States Pharmacopoeia 36

HPLC was used in the analysis for both the identification and Assay with reference to the USP and International Pharmacopeia. The analysis results are therefore tabulated in the tables below

4.1 Table 2; IDENTIFICATION, tests for the presence of API.

SAMPLE	REFERENCE MATERIAL	ACCEPTANCE CRITERIA	RESULT
1A	IP 2011	Must comply to test A and B of IP 2011	Complies
1B	IP 2011	Must comply to test A and B of IP 2011	Complies
1C	IP 2011	Must comply to test A and B of IP 2011	Complies
2A	IP 2011	Must comply to test A and B of IP 2011	Complies
2B	IP 2011	Must comply to test A and B of IP 2011	Complies
2C	IP 2011	Must comply to test A and B of IP 2011	Complies
3A	USP 36	Must comply to test B of USP 36	Complies
3B	USP 36	Must comply to test B of USP 36	Complies
3C	USP 36	Must comply to test B of USP 36	Complies

Table 2shows that all the samples tested had the Active Pharmaceutical Ingredient(API) present. This provides the basis to do further tests as outlined below.

4.2 Table 3;ASSAYtests for percentage content of API

SAMPLE	REFERENCE MATERIAL	ACCEPTANCE CRITERIA	RESULT	COMMENT
1A	IP 2011	90.0% to 110.0%	105.3%	Complies
1B	IP 2011	90.0% to 110.0%	102.3%	Complies
1C	IP 2011	90.0% to 110.0%	101.8%	Complies
2A	IP 2011	90.0% to 110.0%	94.3%	Complies
2B	IP 2011	90.0% to 110.0%	99.0%	Complies
2C	IP 2011	90.0% to 110.0%	95.1%	Complies
3A	USP 36	90.0% to 110.0%	108.2%	Complies
3B	USP 36	90.0% to 110.0%	104.6%	Complies
3C	USP 36	90.0% to 110.0%	102.7%	Complies

Table 3; show the percentage contents of the API with reference to the official monographs. This simply means that the API should not be less than 90% and not more than 110% but within the indicated limits. If it is below the minimum limit, the drug cannot achieve its intended purpose while when above the upper limit, the toxicity and side effect profile equally increases, rendering it not safe for consumption.

4.3 Table 4; APPEARANCE, PACKAGING AND LABLING

SAMPLE	APPEARANCE	PACKAGING	LABLING	RESULT
1A& 2A	Red brick flat tablets with a break line.	Silver aluminiumfoil blister pack of 6 tablets.	Label with correct information for the user.	Complies
1B& 2B	Red brick flat tablets with a break line.	Silver aluminiumfoil blister pack of 6 tablets.	Label with correct and adequate information.	Complies
1C& 2C	Red brick to brown biconvex tablets with a break line.	Silver aluminiumfoil blister pack of 6 tablets.	Label with correct and adequate information for user.	Complies
3A	white viscous suspension	25ml Amber bottle with a screw cap.	Label with adequate information for the user.	Complies
3B	White viscous suspension	25ml Amber bottle with a screw cap.	Label correctly explains information for the user.	Complies
3C	Translucent-white viscous suspension	250ml HDP cylindrical container with an HDP screw cap.	Label present with sufficient information.	Complies

All the samples complied with the official monographs pertaining appearance, labeling and packaging, as shown in table 4 above.

CHAPTER 5

5.0 DISCUSSION

This cross sectional study conducted in Livingstone district of Zambia assessed the quality of selected pediatric HIV/AIDS and TB medicines. The results of the study provide objective information on the quality of drugs being used in the prevention and treatment of HIV/AIDS and TB.

The drugs selected in the study were RH tablets and NVP suspension using HPLC for identification and Assay as well as visual inspections for labeling, appearance and packaging with reference to the official monographs stated above.

The identification tests for the individual samples that were analyzed yielded positive results for all the samples that were tested. This simply means that all the samples passed the identification test and therefore had the API present in them as outlined on the label claim of each of the samples. 100% of the samples tested therefore passed.

The identification test gives you a green light to further your analysis. It is then that the percentage content is done as well as test for impurities in the samples.All the samples under study had 100% compliance to the official monographs with regards to the percentage content of the API. The correct content of the API assures you that the ailment intended to be treated or cured will surely be because we are sure that the drug is present in recommended and adequate amounts.

Packaging plays an important role in ensuring safety and quality of medicines, because if a product is not properly packaged, it may allow foreign particles or an impurity which automatically compromises the quality of the medication. Poor packaging may equally accelerate deterioration of a medicine due to oxidation, light, moisture, temperature and many other factors which may interfere with the chemical composition of the API. The general or physical appearance of a medicine is equally crucial in ascertaining product quality to the public or population. A product that is poorly or improperly appearing is automatically not ideal for consumption as its pharmaceutical and pharmacokinetic properties may have been altered. Public confidence in such a product is also affected basically because of its poor physical appearance.

100% of the samples in this study were correctly appearing and packaged in conformity to the official monographs.

Labels are meant to ascertain the product to the public or consumer that the product actually contains the said API in specified amounts, its intended use, date of manufacturing, date of expiry, batch number, manufacturer license number, storage conditions, medicine category as well as the name and address of the manufacturer. It is actually a legal requirement in Zambia that all medicines are labeled to depict the stated specifications above. It is prudent to mention that 100% of the products tested complied with the labeling standards as outlined in the official monographs as well as the legal requirements of the Republic of Zambia.

The results provide objective evidence that the pediatric HIV/AIDS/TB medicines selected are of good quality and therefore meet the outlined requirements of the official monographs. This is contrary to the studies by Zyambo (2008) and Mweemba (2011) which found counterfeit medicines to be present and ranging from 5% to 20%. The study by Munkombwe (2011) did not find any counterfeit medicines which conform to the findings of this study.

CHAPTER 7

7.0 CONCLUSION

As outlined in the discussion above, it is clear thatthe selected pediatric HIV/AIDS/TB medicines were correctly identified, contained the API in recommended amounts, had the proper appearance and properly packaged. Therefore, it can be concluded that the selected pediatric medicines available in Livingstone District Health facilities of the Republic of Zambia are of good quality and meet the requirements as stipulated in the official monographs of the USP and IP.

Although the results point in the right direction regarding counterfeit drugs, more needs to be done by the regulatory bodies to ensure that no substandard, fake or counterfeit medicines are available on the Zambian market especially in the private health sector. It is encouraging to note that the Zambian Government is planning to Brand all its medicines in a bid to curb the problem of counterfeiting as well as pilferage from its health institutions (MOH, 2013). This is a major step since suppliers will be made to brand the products to meet the government requirements.

7.1 RECOMMENDATIONS

- The result of this study point in the positive direction regarding counterfeit drugs, but a further larger and probably national study is needed to asses this problem at national level.
- Quality assurance tests are of great concern to public health as the public may be subjected to consuming unwarranted medicines. It would be prudent for PRA to decentralize its services to all major towns especially the port of entries and borders just to ensure safety of medicines for public health protection.
- Simple and free text messages can be used to check the authenticity of drugs by either confirming registration with PRA or Manufacturers encrypted codes by any suspecting user.
- Truscan, a hand held spectrophotometer can also be used at airports, borders and any other place to analyze the chemical composition of drugs which helps the on spot detection of counterfeit drugs.

7.2 LIMITATIONS TO THE STUDY

- HPLC is a very expensive quality analysis technique which in a way affected the number of medicines selected for the study due to the high cost of the analytes.
- It is important to note that not all factors that affect the quality of medicines were considered for the study as others such as, transportation, GMP, storage etc were not taken into consideration.

CHAPTER 8

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APPENDICES

APPENDIX I

GANTT CHART

Description of activity	Oct 2012	Nov 2012	Dec 2012	Jan 2013	Feb 2013	Mar 2013	Apr 2013	May 2013	Jun 2013	July 2013	Aug 2013
Research proposal writing											
Research proposal presentation to graduate forum and ERES CONVERGE IRB											
Data/ sample collection											
Data/ sample analysis											
Research report writing											
Submission of research report											

APPENDIX II

Data collection tool

Name of Health facility:_____Date:_____

S/N	Drug information	particulars	Comments/remarks
1.	Name indicated on the product package		
2.	Batch number as indicated on the label		
3.	Active ingredients as indicated on the label		
4.	Product physical appearance		
5.	Nature and material of package		
6.	Manufacturing date		
7.	Expiry date		
8.	Instructions on the label for the use of the product		
9.	Manufacturer and address as stated on the label		
10.	Date of collection of sample		

APPENDIX III

BUDGET

Description	**Responsible person**	**Daily allowance**	**Number of personnel**	**Duration of activity**	**Total cost (ZMK)**
Personnel emoluments	Research assistants	50,000= each	2	10 days	1,000,000=
	Laboratory quality control Analysis	1,000,000=	1	10	10,000,000=
	Principle investigator(accomodation, food and transport to and from L/stone)	300,000=	1	15	4,500,000=
	Research statistcian	200,000	1	5	1,000,000=
				Subtotal	**16,500,000=**
Supplies	**Item**	**Quantity required**	**Unit cost**		**Total cost**
	Ream of paper	4	35,000		150,000=
	Ball point pens Pencils Stapler and stapler Reagents Hiring of laboratory facility Sample purchase contingency	5 3 1 set unit 430	2,000 1,500 120,000 3,000,000 2,500,000 0000000 1,000,000		10,000= 1,500= 120,000= 3,000,000= 2,500,000= 0,000,000= 1,000,000=
				GRAND	**ZMK**

				TOTAL	**23,281,500.** **KR23,281.50=**