CHAPTER 1: INTRODUCTION

1.1 Description of the HIV/AIDS status in Zambia
Zambia a nation with a population of about 12.2 million (CSO 2000), is one of the countries hardest hit with the HIV/AIDS epidemic in the world (MOH & NAC 2008). Although the basic Knowledge about HIV/AIDS stands at 99% among the adult population aged 15 to 49, according to the 2007 Demographic and Health Survey, the national prevalence rate reduced only slightly from 15.6% in 2001/2002 to 14.3% in 2007. The prevalence rate has also remained significantly higher in urban areas (23.1% in 2001/2002 and 19.7% in 2007) compared with rural areas (10.8% in 2001/2002 and 10.3% in 2007) (CSO & MOH 2007).

1.2 Quality issues concerning antiretroviral medicines (ARVS)
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. They saw that their own products were being copied. 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 of substandard drugs, the Food and Drug Administration in the United States of America estimates that worldwide sales of fake drugs exceed US$ 3.5 billion per year, according to a paper published in the journal PLoS Medicine in April 2005. The Center for Medicines in the Public Interest in the USA predicts that counterfeit drug sales could reach US$ 75 billion globally in 2010 if action is not taken to curb the trade (WHO 2006).

According to WHO, drugs commonly counterfeited include antibiotics, antimalarials, hormones and steroids. 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).
Counterfeiters take inert ingredients such as chalk, and even dangerous chemicals, package them convincingly and sell them to consumers. Such drugs may have no therapeutic effect and can be toxic. Although much counterfeit drug trade occurs in the unregulated market of unofficial drug vendors, especially in developing countries, counterfeit drugs are also found extensively in licensed pharmacies.

A number of factors make ART an attractive target for counterfeiters, especially: high unit costs and long-term, sustained demand. In addition, stigma and fear of loss of confidentiality in health care settings increase demand for ARVs delivered through often poorly regulated private sector health care providers, pharmacies or other channels.

### 1.3 Consequences of Substandard drugs

Substandard drugs may have little or no therapeutic value, causing illness and death from the condition supposedly being treated. A substandard drug may be a drug of poor quality or a counterfeit. Fake drugs may be composed of toxic substances that directly cause illness and death. Counterfeited drugs with the appropriate active ingredients in subclinical amounts can also lead to prolonged illness or death, but pose the further risk of encouraging the spread of drug resistant pathogens. It was suggested that treatment failure and drug resistance are possible consequences of the use of sub-standard drugs (Shakoor et al 1997).

Counterfeit drugs pose many far-reaching threats to overall global health. They put individuals at risk of experiencing adverse events or not achieving treatment goals, and also contribute to public health by aiding in the spread of infectious diseases. The prevalence of substandard or fraudulent medications threatens the relationship between patients and their prescribers, pharmacists, and other suppliers. Patients may begin to lose faith in modern medicines altogether if they are harmed or if they do not benefit from them and may cause some people in developing countries seeking alternative medicines such as traditional remedies. Fraudulent activity also threatens the strength of the global marketplace, causing various parties in the supply chain to become distrustful of others, and possibly contribute to nationalism.
1.4 Challenges in Reporting the Health Effect of Substandard Drugs

As of now, very limited data exist from developing countries to help quantify the health effects of substandard ARV drugs. It is also important to mention that due to its discretionary nature, substandard drugs are highly underreported. This is due not only to the fact that not all fraudulent products are identified, and governments in developing countries do not have the resources and capacity to fully regulate the market, but also because there are certain media-related barriers to reporting incidents.

Pharmaceutical manufacturers are extremely reluctant to publicize reports of substandard medications, because consumers may begin to lose confidence in the brand name if they fear that the product may not be authentic. Prescribers and consumers may also believe that the brand name manufacturer is failing in their security measures if they view their products as being easily counterfeited. Not only are manufacturers hesitant to report suspected substandard drugs to the public, but governmental agencies may also be reluctant. They may fear that their regulatory authority may seem insufficient or that they are not upholding their responsibility of protecting citizens from harm and fraud.

Whether people learn about substandard drugs from the media, the government, or have a personal experience with such products, there is another very detrimental consequence that may often be overlooked. People may begin to lose faith not only in certain brand names, but also in the value of taking drugs altogether to treat their illnesses. This could be especially dangerous in developing countries, where infectious diseases are much more prevalent. If patients decide not to take medications due to distrust of manufacturers, governmental agencies, or health care professionals, they not only endanger their own health, but it also becomes a greater public health concern if they remain infectious. This can also be a bigger problem in developing countries since people often spend more of their income on pharmaceuticals, and they may be less likely to spend their already limited income on drugs that may be ineffective or potentially harmful. Developing counties may not easily rise to the challenges discussed above, the principal reason being, the developing countries are still addressing the problem at a much earlier stage of economic development than the presently developed countries.
1.5 Research Gaps
In the last few years governments around the world have pledged to massively scale up the delivery of antiretroviral drugs (ARVs) to achieve universal access for all. To date attention has focused on how to finance this effort and how to strengthen health care delivery systems, including how to conduct mass HIV testing programs and increase the number of health care providers worldwide. Less attention has been paid to the responsibilities of governments and international agencies to address the widespread prevalence of substandard medicines and the threat of counterfeit ARVs.

Generic antiretroviral (ARV) medications have recently become available in many developing countries and Zambia is not an exception. The cost of these medications now is by far cheaper than discounted proprietary agents. However, recent reports of generic medications including ARVs containing little or no active ingredients are disturbing and it calls for studies in drug content analysis. (Apoola et al 2001). There is currently insufficient publicly available data describing the ARV drug content in reference to label claim or substandard ARVs in Zambia.

1.5 Dissertation Focus
This dissertation was under-taken with a view to assess the quality of ARVs dispensed in health facilities in Lusaka District with regard to the set standards as prescribed in official monographs of British Pharmacopoeia (BP) and United States Pharmacopoeia (USP). In this study the researcher analyzed the content of some first-line generic and proprietary ARV formulations in Lusaka. Therefore, this research study conducted in Lusaka did not only help to assess the prevalence of substandard ARV drugs, but also inform policy at a crucial stage in the evolution of Zambia’s pharmaceutical landscape. In addition to informing policy and assisting in planning cost-effective interventions, this study in Lusaka has also helped to bridge the knowledge gap in understanding the prevalence of substandard ARV drugs that has existed far too long in Zambia.
CHAPTER 2: STATEMENT OF THE PROBLEM

It has been observed that little is known as regards quality of ARVs that are dispensed in Zambia and Lusaka District in particular. Equally, there is little information as to whether there are substandard ARVs on the Zambian market.

There is currently no available literature on quality of ARVs dispensed in Zambia. However, some work has been done in the region and developed countries on ARVs as well as other drugs. Prevalence of substandard drugs in the global marketplace is reaching epidemic proportions; with developing countries disproportionately affected to a greater degree (Quick et al 1997).

A recent survey by the WHO of seven African countries found that between 20 and 90 per cent of all anti-malarials failed quality testing. These included chloroquine-based syrup and tablets, whose failure rate range from 23 to 38 per cent; and sulphadoxine / pyrimethamine tablets, up to 90 per cent of which were found to be below standard (WHO 2007).

There is limited data on the effectiveness of HAART in developing countries (UNAIDS 2008), despite the fact that 60% of the World’s 42 million with HIV/AIDS live in the sub-Saharan Africa and the region has the highest number of deaths due to HIV/AIDS (Severe et al 2008).

If drugs contain too little of the active ingredient, not all 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 pills or because the delivery vehicles are inappropriate. As a result, patients receive too little medicine and die or are far sicker than would have been the case if they had received an adequate dose.

In Zambia, anecdotal data show that there is an increase in morbidity and mortality in people living with HIV/AIDS due to ARV drug resistance, treatment failure and adverse drug effects. Ceasar Mudondo, then chairman of Zambia’s Poisons and Pharmacy Board was reported having said that the uncontrolled selling of ARVs on the black market, street corners and clinics made it very difficult to monitor people on ARVs. He further stated that it was knocking back AIDS
research because of new strains of HIV. A physician of the UTH confirmed that his eight patients did not respond to any combination after developing resistance to ARVs (Geloo 2005).

According to the reviewed literature in this study, it is evident that the issue of substandard medicines is a global one. Quality analysis of drugs is very important but it is a costly venture especially in developing countries like Zambia and this is the main reason why routine checks on the quality of medicines are rarely done. Substandard drugs pose an enormous threat to public health globally.

Therefore, it is also possible that there could be substandard drugs of ARVs in Zambia. It is therefore, necessary to routinely monitor the quality of all pharmaceuticals that are locally manufactured and those imported or donated to ensure that they meet the set international and national standards. If this area is neglected Zambia will be wasting a lot of money in distributing to its people substandard medications which may do more harm than good to its people.

2.1 Problem Analysis
According to WHO, factors that have been suggested to contribute to the production of substandard drugs 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). Displayed below is a problem analysis diagram depicting factors associated with substandard ARVs.
Figure 2.1: Problem Analysis Diagram

Problematic issues related to substandard ARVs.

- Lacking of therapeutic effect and treatment failure (Bate and Boateng 2007).
- Complications and mortality due to disease and toxic components of the drugs (Kelesidis et.al 2007).
- High burden of disease leading to mortality and morbidity (Kelesidis at.el 2007).
2.2 Research Questions

1. Does the quality of ARVs dispensed in health institutions in Lusaka District meet the set standards as prescribed in the official monographs? (E.g. drug content of an individual tablet within 80 to 100% of the label claim).

2. Can there be any substandard ARVs dispensed in Zambian health facilities?

2.3 Rationale

It is envisaged that the findings of this work might contribute to the body of knowledge as well as help in formulating of strategies that might be employed to enhance and strengthen the regulatory and law enforcement institutions in fighting substandard ARV drugs, thereby contributing to the control of HIV/AIDS in Zambia. It is expected that successful control of HIV/AIDS will result in increased productivity, enhanced economic growth and reduced poverty levels, hence contributing towards attaining of MDG number 6 by 2015.

2.4 Hypothesis

The quality of ARVs dispensed in health facilities in Lusaka District meets the set standards as prescribed in official monographs of BP and USP.

2.5 General Objective

To determine the quality of some ARVs dispensed in health facilities and to assess the proportion of substandard ARVs in Lusaka District.
2.6 Specific Objectives

i. To verify the active ingredients contained in samples of (1) Stavudine (d4T)/Lamivudine (3TC)/Nevirapine (NVP), (2) Lamivudine (3TC)/Zidovudine (AZT), (3) Nevirapine (NVP), (4) Efavirenz (EFV) and (5) Stavudine (d4T)/Lamivudine (3TC).

ii. To evaluate the percentage content of the active ingredients in (1) d4T/3TC/NVP, (2) 3TC/AZT, (3) NVP, (4) EFV and (5) d4T/3TC.

iii. To assess the packaging and labeling standards on the containers in samples of (1) d4T/3TC/NVP, (2) 3TC/AZT, (3) NVP, (4) EFV and (5) d4T/3TC.

iv. To determine the proportions of substandard drugs in the samples of (1) d4T/3TC/NVP, (2) 3TC/AZT, (3) NVP, (4) EFV and (5) d4T/3TC.

v. To make recommendations to the Ministry of Health (MoH) through Pharmaceutical Regulatory Authority (PRA) pertaining the quality of ARVs in Lusaka District.

2.7 Justification of the study

Generic and discounted brand name antiretroviral (ARV) medications are becoming increasingly available in developing countries including Zambia. To date, little information is available on drug content versus label claims for these medications.

There is no available documentation on the prevalence of counterfeit ARVs in Zambian and yet the country is faced with issues of ARV drug resistance, increased side effect profile and treatment failure for patient on antiretroviral therapy (ART) resulting in mortality.

The purpose of this study was to assess drug content compared to the labeled amount among ARV obtained from health centers in Lusaka District. No research concerning quality of ARVs has been done in Zambia and yet Zambia is one of the first African countries to be subjected to the life prolonging Anti-Retroviral drugs (ARVs) trials a decade ago. The following chapter presents a review of the prevalence of substandard drugs of existing available literature globally, regionally and locally.
CHAPTER 3: LITERATURE REVIEW

3.1 Global Perspective
The prevalence of substandard or counterfeit drugs in the global marketplace is reaching epidemic proportions; with developing countries disproportionately affected to a greater degree (Quick et al 1997). The security measures and tests that can be employed to identify substandard drugs can be extremely costly and difficult to implement. Many countries especially in resource limited countries do not have enough resources to use consistently for such purposes. In addition to these issues, the general demand for pharmaceuticals can be much higher in developing countries than in developed countries, particularly for life-threatening conditions. These needs can create a sense of urgency and desperation, causing people to sacrifice more to attain the treatments that they believe will save their lives and those of their families. The combination of these factors ripens the atmosphere in developing countries for drug counterfeiting.

Due to the difficult nature of identifying substandard drugs, estimates on prevalence are not precise, but they give valuable insight to the scope of the problem. The World Health Organization has estimated that approximately 10 percent of the global pharmaceuticals market consists of substandard drugs, but this estimate increases to 25% for developing countries, and may exceed 50% in certain countries (WHO 2008).

Considering that approximately 40 million people are living with HIV today (WHO 2007), this presents enormous opportunities for drug counterfeiters to profit without easily being exposed. Anti-retroviral drugs (ARVs) used in the treatment of HIV and AIDS are targets that have the potential for the greatest global impact, but other diseases and conditions are always possible targets as well.

3.2 Regional Perspective
Substandard antiretroviral drugs were found in Lubumbashi, Congo (DRC) in December 2003. The bottles and blisters which were not in carton boxes were labeled ‘Triomune’ (stavudine, lamivudine and nevirapine) and ‘Duovir’ (lamivudine and zidovudine), both of which are Cipla’s
brand products. Preliminary investigations showed that fake labels were put on bottles containing non-ARV pharmaceutical products. Some tablets have been identified to contain fluvoxamine (antidepressant) or cyclobenzaprine (muscle relaxant). Counterfeiters have targeted health prescribers and patients to buy these cheap ARVs (Ravinetto 2004).

HIV/AIDS treatment is also under threat from counterfeit medicines. The recent discovery of counterfeit antiretrovirals (stavudine-lamivudine-nevirapine and lamivudine-zidovudine) in the Congo (Ahmad 2004) raises the prospect that the first line therapies for treatment of HIV/AIDS could soon be rendered useless.

Medecins Sans Frontieres (MSF), which is running an HIV/AIDS program in the DRC, reported that fluvoxamine (an antidepressant) and cyclobenzaprine HCl (a muscle relaxant) had been labeled as either ‘Triomune’ or ‘Duovir’, the two commonly prescribed antiretroviral brands that are manufactured by Indian pharmaceutical company Cipla (Lancet 2004).

Ethiopian health officials warned the public not to buy counterfeit ARVs. Smugglers were illegally importing drugs and passing them off as antiretroviral drugs. According to Ethiopia’s Drug Administration and Control Authority, these illegally imported drugs were of unauthorized quality and with unpredictable effects (Kaisernetwork.org 2003).

In Ivory Coast a drug called Ginovir 3D capsule was found be counterfeited. Ginovir 3D capsule is antiretroviral combination product consisting of zidovudine 200 mg, lamivudine 150 mg, and indinavir 40 mg). The WHO received information about the availability of a counterfeit version of this antiretroviral triple combination product. Analysis of the fake drug was done by the Agence Francaise de Securite Sanitaire des Produits de Sante (AFSSAPS) upon request from the Association of AIDS Patients (AIDES). Results showed the samples did not contain lamivudine or indinavir; they contained zidovudine 201 mg, stavudine 40 mg, and an unidentified substance. The manufacturer on the label was Selchi Pharmaceuticals, Namibia (. WHO QSM/MC/IEA 2003).

The Daily Nation newspaper of Kenya reported that antiretrovirals for distribution as part of Kenya’s AIDS medicine program were being sold on the black market in Nairobi. The drugs are
being sold at less than US$65 for a monthly cocktail (Siringi 2004). In Zimbabwe, an HIV-infected man was reported to purchase zidovudine that turned out to contain no active ingredient upon analysis (Apoola et al 2001).

3.3 National Perspective
In Zambia, a 'cure' for AIDS called Tetrasil was promoted by a Zambian newspaper editor who held an ownership stake in the product with a prominent US AIDS denialist. The product was found to be a pesticide used to clean swimming pools (Medical News Today 2007). Some people living with HIV/AIDS abandoned their ART for the drug (Kaunda 2007).

Viracept (nelfinavir) an antiretroviral drug was developed through a joint venture in the 1990s involving Aguoron Pharmaceuticals and Japan Tobacco. This drug was approved for its therapeutic use by US Food and Drug Administration two decades ago. On 6th June 2007, an alert was issued by both the European Medicines Agency and Health Care Products Regulatory Agency, stating that a recall must be instituted after certain batches of viracept were thought to contain chemicals that could potentially cause cancer. Zambia’s Pharmaceutical Regulatory Authority (PRA) quickly undertook random checks in the country to ensure that the cancer-linked viracept was no longer in circulation. At the time of recall in Zambia 100 patients were prescribed it. (Fiddian 2007).

In a related study done in Zambia entitled “Evaluation of the quality of cotrimoxazole, paracetamol and pyrimethamine/sulphadoxine tablets manufactured by local pharmaceutical companies in Lusaka” it was reported that 25% of the cotrimoxazole tablets sample assayed did not comply with B.P 1993 specifications for active ingredient percentage content (92.5 to 107.5%) (Zyambo 2008).
CHAPTER 4: RESEARCH METHODOLOGY

4.1 Study Design
A cross-section survey was conducted in nine health facilities of Lusaka District, using convenience sampling technique. A quantitative study design was used. The study used quantitative design because the research tested the relationship and differences among and between variables using numbers. These processes were tested with hypotheses and research questions (Wood and Haber 2002).

4.2 Study Setting
Zambia is one of the countries with hyper epidemic levels of HIV. This study was conducted in Zambia’s capital City Lusaka. Zambia is a landlocked country situated in South Central Africa with a population estimated to be approximately 12.2 million according to central statistical office (CSO 2000). Lusaka its capital City has an estimated population of 2 million people (CSO 2000), having the largest population of all the nine provinces of Zambia.

Figure 4.1 Map of Zambia

<table>
<thead>
<tr>
<th>Health Centers</th>
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<tbody>
<tr>
<td>1. Chelstone</td>
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<tr>
<td>2. Mtendere</td>
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<tr>
<td>3. Kalingalinga</td>
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<tr>
<td>4. Bauleni</td>
</tr>
<tr>
<td>5. Kabwata</td>
</tr>
<tr>
<td>6. Kamwala</td>
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<tr>
<td>7. Makeni</td>
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<tr>
<td>8. Kanyama</td>
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<td>9. Matero</td>
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</table>
In order to have a good sample size, the study was undertaken in Lusaka District. This is where most of the public health facilities in Lusaka province are concentrated. This setting provided the researcher with easy access to drug sample collection. Furthermore, Lusaka province has HIV prevalence level of 20%. The prevalence is much higher among residents of Urban than Rural areas (19.7% Vs 10.3%) (CSO 2000).

The drug samples were collected from public health facilities. A few were selected randomly in different clusters of the District. The quality analysis of these ARVs was carried out using Thin Layer Chromatography (TLC) at Tejay Pharmaceutical laboratories in Lusaka.

4.3 Study population
The study population comprised 4 x 60 tablets Lamivudine/Zidovudine 150/300mg, 2 x 30 tablets Efavirenz 600mg, 2 x 60 tablets Nevirapine 200mg, 2 x 60 tablets Lamivudine/Stavudine/Nevirapine 150/30/200mg, and 1 x 60 tablets Stavudine/Lamivudine 30/150mg which were randomly selected from nine public health facilities of Lusaka. This sample was drawn from health facilities of Lusaka District, using convenience sampling technique. It included nine public institutions conveniently selected from the clusters of the District. The District was divided into 4 geographical clusters, and from each cluster at least 2 public health facilities were selected. Namely cluster 1 (Chelston and Mtendere), cluster 2 (Kalingalinga and Bauleni), cluster 3 (Kabwe, Kamwala and Makeni), and cluster 4 (Kanyama and Matero).

4.4 Inclusion Criteria
Only first-line ARVs were included in the study, as long as they were not expired, with reference to the expiry date on the label.
Public health facilities where ARVs are dispensed were included.

4.5 Exclusion Criteria
Second-line ARVs and all drugs not used as first-line in the management of HIV/AIDS. ARVS drugs that had less than six months shelf-life were not included in the study.
Public health facilities which do not dispense ARVs were excluded.
4.6 Sampling Methods
The multistage sampling method was employed in the collection of ARVs for analysis. This involved a successive convenient sampling of clusters that met sample eligibility criteria. The first – stage sampling consisted of large clusters. The second – stage sampling consisted of units. Third – stage random sampling of tablets (Wood and Haber 2002).

4.7 Sample Size Determination
Samples of eleven ARVs were selected using the probability, multistage sampling method. The study was designed to tolerate an absolute sampling error of up to 5%, with confidence interval at 95%.

The following formula was used to calculate the sample size.

\[ n = \frac{Z^2 P (100-P)}{d^2} \]

where:-
- \( Z = 1.96 \), the factor from the normal distribution.
- \( P \) = Expected period prevalence.
- \( d \) = Absolute sampling error.
- \( n \) = Sample size.

Therefore \( n = (1.96)^2 \times 50(100-50)/5^2 = 384 \) tablets.

Adjustment for handling loses was set at – 10%

= 422 tablets of ARV Medicines but rounded upwards to 430

Since the total samples size was 430 tablets, 48 sample tablets were collected from each health facility under study in Lusaka District.

4.8 Data Collection Tools
The instrument of research was a drug collection sheet, with sections, relating to the general information of the institution and drug information including the date, the name of the drug indicated on the product package, identification number of the drug, active ingredient(s) contained in the product as indicated on the packaging, physical appearance of tablets, nature and material of packaging material, appearance of the label on the packaging, instructions on the label for the use of the product, manufacturing date as stated on the product label, batch number
of the product as stated on the label, and manufacturer of the product and address as stated on the label.

4.9 Data collection Techniques
Samples of drugs from the public institutions were obtained with permission from the Permanent Secretary, Ministry of Health and Lusaka District Health Management Team (LDHMT). Data were collected after carrying out the analysis of the study units using the laid down procedures in a concise Quality Control Guide on Antiretrovirals of Pharmaceutical Regulatory Authority, Ministry of Health of Zambia. This protocol is adapted from German Pharm Health Fund, Frankfurt (October 2003). It is accessible on internet: www.gphf.org. The data were collected over the period of 12 weeks from the date of approval from the University of Zambia Biomedical Research Ethics Committee (UNZA BREC).

4.10 Validity and Reliability of the Results
Validity was ensured by covering all important variables (see 4.14) under this study. A pre-test of the instrument (GPHF min-lab) was conducted and amendments to the instrument were done.

4.11 Data Quality Control Checks
The researcher worked closely with the Drug laboratory Analyst Manager at Tejay Pharmaceuticals Limited. Technical expertise regarding the use of laboratory equipment was sought accordingly. The researcher was involved in the analysis and monitored data quality immediately after each sample analysis. Tests were repeated three times where results did not show consistency that is where the principal spots did not correspond in terms of color, size, intensity and travel distance. This was in order to ensure quality data of analysis.

4.12 Ethical Consideration
Even if this study does not directly deal with human participants, clearance was sought from the University of Zambia Biomedical Research Ethics Committee (UNZA BREC). Permission was also sought from MOH for collection of samples from health institutions. The different brands of some first-line HIV/AIDS medications which were analyzed were coded as 1A, 1B, 1C, 1D, 2A,
2B, 3A, 3B, 4A, 4B, and 5A. These codes denote different batch numbers of drug samples which were used in the analysis. They were used in the interpretation of the results.

4.13 Data Processing and Analysis
Data was analyzed using percentages, proportions and Chi-square tests through the SPSS version 16.0 for windows. Pearson Chi-square test was used to test the hypothesis of the study. The analysis was based on comparing the treatment group results with standard references.

4.14 Variables of the Study

Independent variables
- Active ingredients
- Percentage content
- Packaging and
- Labeling

Dependant variables
- Reference standards
### Table 1: Variables and indicators

<table>
<thead>
<tr>
<th>Variables</th>
<th>Indicators</th>
<th>Scale of measurement</th>
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<tbody>
<tr>
<td>Active Ingredient in the samples</td>
<td>Distance of principal spots under UV light of 254nm</td>
<td>Principal spots corresponding in size and travel distance relative to lower and higher standards</td>
</tr>
<tr>
<td>Percentage content of active ingredients in the samples</td>
<td>Colour and intensity of principal spots observed under UV light of 254nm</td>
<td>Difference in color and intensity of principal spots relative to lower and higher standards with concentrations of 80 and 100% respectively</td>
</tr>
<tr>
<td>Packaging and labeling of drug sample containers</td>
<td>Information according to packaging and labeling standards</td>
<td>Drug samples with missing or incorrect accompanying documents and defective packaging or incomplete, damaged or missing labels</td>
</tr>
<tr>
<td>Reference standards of ARVS</td>
<td>Standards of Stavudine(d4T), Nevirapine (NVP), Lamivudine (3TC), Zidovudine (AZT), and Efavirenz (EFV) with lower and higher concentrations at 80 and 100%</td>
<td></td>
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<tr>
<td>Code</td>
<td>Name/ Strength</td>
<td>Batch/Lot Number</td>
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</tr>
<tr>
<td>1A</td>
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<tr>
<td>1D</td>
<td>Lamivudine/Zidovudine 150/300mg</td>
<td>LZ 1509094-A</td>
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<tr>
<td>2A</td>
<td>Efavirenz Tablets 600mg</td>
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CHAPTER 5: RESULTS OF THE STUDY

In this study a total of eleven (11) ARV-drug samples were collected from nine (9) health facilities in Lusaka District. All the samples were first-line HIV/AIDS medicines of which the general details are given in table 2 above. On average they had an expiration date of at least 24 months, which is usually considered to be good expiration date for ARVs. Data collected was cross tabulated.

Table 3: Quantity of Nevirapine (NVP) expressed as a percentage

<table>
<thead>
<tr>
<th>Percentage Content of NVP in Samples</th>
<th>&lt; 80%</th>
<th>80%</th>
<th>80% – 100%</th>
<th>100%</th>
<th>&gt; 100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>*LL-RS</td>
<td>NVP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3A</td>
<td>NVP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3B</td>
<td>NVP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4A</td>
<td>NVP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4B</td>
<td>NVP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*UL-RS</td>
<td>NVP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*LL-RS Lower Limit Reference Standard
*UL-RS Upper Limit Reference Standards

Table 4: Quantity of Efavirenz (EFZ) expressed as a percentage

<table>
<thead>
<tr>
<th>Percentage Content of EFZ in Samples</th>
<th>&lt; 80%</th>
<th>80%</th>
<th>80% – 100%</th>
<th>100%</th>
<th>&gt;100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>*LL-RS</td>
<td>EFZ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2A</td>
<td>EFZ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2B</td>
<td>EFZ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*UL-RS</td>
<td>EFZ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*LL-RS Lower Limit Reference Standard
*UL-RS Upper Limit Reference Standards
Table 5: Quantity of Stavudine (D4T) expressed as a percentage

<table>
<thead>
<tr>
<th>Percentage Content of D4T in Samples</th>
<th>&lt; 80%</th>
<th>80%</th>
<th>80% – 100%</th>
<th>100%</th>
<th>&gt;100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>*LL-RS</td>
<td>D4T</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4A</td>
<td>D4T</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4B</td>
<td>D4T</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5A</td>
<td>D4T</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*UL-RS</td>
<td></td>
<td></td>
<td>D4T</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*LL-RS Lower Limit Reference Standard

*UL-RS Upper Limit Reference Standards

Table 6: Quantity of Zidovudine (AZT) expressed as a percentage

<table>
<thead>
<tr>
<th>Percentage Content of AZT in Samples</th>
<th>&lt; 80%</th>
<th>80%</th>
<th>80% – 100%</th>
<th>100%</th>
<th>&gt;100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>*LL-RS</td>
<td>AZT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1A</td>
<td>AZT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1B</td>
<td>AZT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1C</td>
<td>AZT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1D</td>
<td>AZT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*UL-RS</td>
<td></td>
<td></td>
<td></td>
<td>NVP</td>
<td></td>
</tr>
</tbody>
</table>

*LL-RS Lower Limit Reference Standard

*UL-RS Upper Limit Reference Standards
Table 7: Quantity of Lamivudine (3TC) expressed as a percentage

<table>
<thead>
<tr>
<th>Percentage Content of 3TC in Samples</th>
<th>&lt; 80%</th>
<th>80%</th>
<th>80% - 100%</th>
<th>100%</th>
<th>&gt;100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>*LL-RS</td>
<td>3TC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1A</td>
<td>3TC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1B</td>
<td>3TC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1C</td>
<td>3TC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1D</td>
<td>3TC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4A</td>
<td>3TC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4B</td>
<td>3TC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5A</td>
<td>3TC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*UL-RS</td>
<td></td>
<td></td>
<td></td>
<td>3TC</td>
<td></td>
</tr>
</tbody>
</table>

*LL-RS Lower Limit Reference Standard
*UL-RS Upper Limit Reference Standards

Tables, 3,4,5,6 and 7 above, show data obtained from the chromatograms. They depict both qualitative and quantitative data as detected API and percentage content of API in the samples respectively.

The recommended range of reference standards for each active ingredient is 80 – 100%, outside this standard range indicates deviation from reference standards.

None of the samples was found to contain excess amounts (>100%) of the active ingredient(s). The majority of the samples had their percentage content within the recommended range (80-100%). Only one sample was found to contain less amount of the API (< 80%).
### CHAPTER 6: INTERPRETATION OF THE RESULTS

Table 8: Number of API in single and combinations of ARV drug samples

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
<th>Content within 80-100%</th>
<th>Content Below 80%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT</td>
<td>Count</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>3TC</td>
<td>Count</td>
<td>7</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>EFZ</td>
<td>Count</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>NVP</td>
<td>Count</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>D4T</td>
<td>Count</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
<td>19</td>
<td>1</td>
<td>20</td>
</tr>
</tbody>
</table>

Table 8, shows the number of individual active pharmaceutical ingredient analyzed. A total of 20 active ingredients were analyzed from 11 drug samples obtained from the field.
Table 9: Identification of API in ARV Drug Samples

<table>
<thead>
<tr>
<th>Drug Sample Code</th>
<th>Comment</th>
<th>API Present</th>
<th>API Absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A AZT 3TC</td>
<td></td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>1B AZT 3TC</td>
<td></td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>1C AZT 3TC</td>
<td></td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>1D AZT 3TC</td>
<td></td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>2A EFZ</td>
<td></td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2B EFZ</td>
<td></td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>3A NVP</td>
<td></td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>3B NVP</td>
<td></td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>4A NVP D4T 3TC</td>
<td></td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>4B NVP D4T 3TC</td>
<td></td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>5A D4T 3TC</td>
<td></td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>20</td>
<td>0</td>
<td>20</td>
</tr>
</tbody>
</table>

Table 9 indicates that all the 20(100%) ARV drug Samples assayed contained Active Pharmaceutical Ingredient (API) as per labeling on the drug containers.
Table 10: Percentage Content of API in ARV Drug Samples

<table>
<thead>
<tr>
<th>Drug Sample Code</th>
<th>Comment</th>
<th>API within 80%-100%</th>
<th>API below 80%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A 1B 1C 1D 2A 2B 3A 3B 4A 4B 5A</td>
<td>AZT 2 0 2</td>
<td></td>
<td></td>
<td>Total 19</td>
</tr>
<tr>
<td>3TC</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>EFZ 1 0 1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>NVP 0 1 1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>NVP 1 0 1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>NVP 3 3</td>
<td>D4T</td>
<td>0 0 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3TC</td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>NVP 3 3</td>
<td>D4T</td>
<td>0 0 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3TC</td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>D4T 2 0 2</td>
<td>3TC</td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

Table 10 shows that only 1(5\%) ARV drug Sample contained less than 80\% API content, while 19(95\%) of the total ARV-drug Samples contained 80-100\% API content.
Table 11: Proportion of compliance of ARVs in the total sample population

<table>
<thead>
<tr>
<th>Generic Drug</th>
<th>Complied</th>
<th>Did not comply</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>3TC</td>
<td>7</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>EFZ</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>NVP</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>D4T</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>19</strong></td>
<td><strong>1</strong></td>
<td><strong>20</strong></td>
</tr>
</tbody>
</table>

Table 11 shows the only 1(5%) of the total sample did not comply with the stipulated specifications.

Table 12: Expiration date and Compliance of ARV drug samples

<table>
<thead>
<tr>
<th>Expiry Date</th>
<th>Complied</th>
<th>Content Below 80%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011 – 06</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>2011 – 09</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>2011 – 10</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>2011 – 11</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>2012 – 04</td>
<td>6</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>19</strong></td>
<td><strong>1</strong></td>
<td><strong>20</strong></td>
</tr>
</tbody>
</table>

Table 12 shows that the drug sample that did not comply had shelf life of 24 months, expiring in October, 2011, which is not a short expiration date.

**Results for compliance to labeling information on the package of drug samples**

The eleven sampled ARV-drugs analyzed for labeling requirements on the package according to Statutory Instrument No. 47 of 1993, two products had 90% compliance while nine had 100% compliance.
Results for compliance to labeling information on the inserts

All the eleven samples scored 100% compliance to labeling information on the inserts. This implies that all the sampled ARV-drugs had the manufacturer’s inserts present in packages which were adequately labeled according to PRA standards as required by law.

Table 13: Association between reference standards and ARV drug Samples

Chi – Square Tests: Testing the Hypothesis

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>Df</th>
<th>Asymp. sig (2 - sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Chi – Square</td>
<td>4.211</td>
<td>4</td>
<td>.378</td>
</tr>
<tr>
<td>Number of Valid Cases</td>
<td>20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Considering the Chi-square tests in table 13, the quality of ARVs dispensed in health Facilities in Lusaka District meet the set standards as prescribed in official monographs (p = 0.378).
CHAPTER 7: DISCUSSION OF FINDINGS
In this section the comments are in line with the stated objectives of this study. However, as a prelude to the discussion, some salient analytical instruments and protocols are discussed, of which the validity of the research findings are the key elements.

A cross-section study was carried out to determine the quality of selected first-line HIV/AIDS medicines dispensed in public health facilities in Lusaka Urban District of Zambia. The drugs evaluated include (1) Stavudine (d4T)/Lamivudine (3TC)/Nevirapine (NVP), (2) Lamivudine (3TC)/Zidovudine AZT), (3) Nevirapine (NVP), (4) Efavirenz (EFV) and (5) Stavudine (d4T)/Lamivudine (3TC) using GPHF-Minilab techniques and the Statutory Instrument No. 47 of 1993.

The GPHF-Minilab
This is a Mini-laboratory developed by the German Pharma Health Fund (GPHF), a non-profit organisation that promotes projects for improvement of health services in developing countries. It is being used by 18 African countries, 15 Asian countries, and 9 Latin American countries. GPHF-Minilab comes with a concise control Guide (Testing procedures) on antiretrovirals (ARVs), antibiotics, and antimalarials. Nevertheless, it does not come with reference standards which are usually purchased separately.

It employs the Thin Layer Chromatography (TLC) to verify the drug’s identity and to verify the drug’s potency (amount of active pharmaceutical ingredient). Reference for details is made in annex III. The Pharmaceutical Regulatory Authority (PRA) Inspectorate Unit, Ministry of Health in Zambia is currently using GPHF-Minilab to detect counterfeit and substandard pharmaceuticals and to provide basic quality controls of drugs.

The GPHF-Minilab control guide was used in this research project because it provides a cost-effective and reliable method of analysis to verify the quality of ARVs in resource limited settings like Zambia. It was also selected because it was the most readily available and that it was envisaged that the findings from this project would be comparable to the previous works of PRA.
The testing procedures on ARVs were adapted from GPHF-Minilab but the research activities (analytical works) were conducted at Tejay Pharmaceuticals of Lusaka. This was so in order to produce an independent work free and away from the influences of the PRA.

Statutory Instrument No. 47 of 1993
The labeling of medicines in Zambia is based on the Statutory Instrument No. 47 of 1993. Labeling of drug products constitutes the quality of the drug formulation. All manufacturing pharmaceutical companies either foreign or local are required by this law to label their drug products as stipulated in this instrument. Crudely presented formulations are considered to be of poor quality. This instrument was used in this research because it was found to be consistent with GPHF-Minilab specifications on labeling.

7.1 Identification and quantification of Active Pharmaceutical Ingredients (APIs) in Samples
Identification refers to the detection of the API in a give sample. It is a very important quality test because it can prevent further unnecessary analyses in cases where a sample does not contain the active ingredient thereby saving on financial resources and time. Quantification means measuring of the amount of the API in the sample. It is usually performed following the identification of the API in the sample under investigation. It is also important in that it provides data on the potency and safety of the drug product.

Zidovudine (AZT)
Upon analysis of zidovudine (AZT) in the samples, the outcome was that all the four samples namely; 1A, 1B, 1C and 1D contained AZT in the right quantities as per label claim on the packaging. These samples were from four different pharmaceutical Indian manufacturing companies. They were of different batch numbers and were all manufactured in 2009 with an expiry date of 2012. It is important to note that usually ARVs have on average an expiration date of 24 months. It is also interesting to observe that these samples were obtained from different health facilities in Lusaka District; these are Kalingalinga, Bauleni, Kamwala and Kanyama.
Lamivudine (3TC)
The determination of 3TC in the seven samples of 1A, 1B, 1C, 1D, 4A, 4B and 5A resulted in the right identification and quantification of 3TC in all of them. 4A and 4B drug samples were also from different Indian pharmaceutical companies, with different batch numbers and were manufactured in 2009, expiring in 2011. These were sampled from Kabwata and Chelston respectively.

Efavirenz (EFZ)
The two samples of EFZ (2A and 2B) analyzed were from the same Indian pharmaceutical company but had different batch numbers. They were also manufactured in 2009 and were expiring in 2011. Kalingalinga and Kabwata are the health facilities from which the samples were obtained. Upon analysis, EFZ was identified and in right amounts. However, it is important to note that unlike the other ARVs, analysis of EFZ requires acetonitrile as one of the reagents for the mobile phase. This made its analysis a bit more expensive than others.

Stavudine (D4T)
D4T was identified and quantified in right amounts as per label claim in three samples; 4A, 4B and 5A. 5A was obtained from Mtendere Health Center. Its manufacture date and expiry were in 2009 and 2011 respectively. The three different batches were employed in the analysis of D4T and all of them passed the test.

Nevirapine (NVP)
Four samples; 3A, 3B, 4A and 4B were analyzed for NVP. NVP was correctly identified in all the samples but when it came to quantification of the API only three samples passed the test. Sample 3A was found to contain less than 80% of NVP content. 3A and 3B were samples from the same Indian pharmaceutical company whose batch numbers were different. The sample in question (3A) was collected from Matero Main Clinic. This sample had good expiry date as shown in Table 2. This implies that its inadequate percentage content had nothing to do with its expiration date.
7.2 Compliance to the labeling requirements of Statutory Instrument No. 47 of 1993

Drug labeling refers to all printed information that accompanies a drug, including the label, the wrapping and the package insert. In Zambia drug labeling is regulated by Pharmaceutical Regulatory Authority (PRA) through the Statutory Instrument No. 47 of 1993. The regulations apply to prescription only drugs, pharmacy medicines and general sale medicines. PRA requires that drug labeling be balanced and not misleading. The label must be scientifically accurate and provide clear instructions to health care practitioners and to consumers.

**Package (labeling on the container)**

The evaluation of compliance was based on the following information; Brand name, Name and strength of active ingredient, Quantity of medicine, Date of manufacture, Expiry date, Batch/lot number, Manufacture licence number, Medicine category, Storage conditions and Name and address of manufacturer. It was observed that sample 1B and 1C both containing AZT/3TC did not reflect medicine category on the package. This means that 18% of the drug samples under study did not meet the requirements of the Statutory Standard on labeling for Zambia. Medicine category refers to prescription only drugs (POMs), pharmacy medicines (P) and general sale medicines (GS). Like other essential medicines 1B and 1C are required by law to show POM on the package. This is because the omission of POM on the package is misleading both to the health practitioners and consumers.

**Package Inserts (manufacturer’s literature)**

Inserts contain necessary supplementary information that cannot be accommodated on the outer package of the drug. The manufacturer’s literature usually includes information on; Name of medicine, Pharmacological properties, Direction of use, Side effects, Contraindications, Warnings and Precautions. The law also requires that this information is depicted on the insert. On this score all samples obtained 100%.

It is interesting to observe that contrary to the report of Apoola et al (2001) and existing anecdotal data in Zambia, this study has provided evidence that first-line HIV/ADS medicines available in Lusaka District are of good quality and meet the requirements of the official monographs.
CHAPTER 8: CONCLUSIONS

Finally, the results discussed and presented above indicate that 100% ARV-drug samples were correctly identified for API and over 94% of the total drug samples contained API in right amounts and that over 90% of these samples were correctly labeled according to the Statutory Instrument No. 47 of 1993 of the Pharmaceutical Regulatory Authority, Ministry of Health in Zambia. Therefore, it can be concluded that first-line HIV/AIDS medicines dispensed in Lusaka District of Zambia are of good quality and meet the requirements as stipulated in the official monographs such as the BP and USP.

Lastly but not the least, substandard and spurious ARV-drugs are a big challenge to health care systems especially in the developing countries. However, it is interesting to note that this study in particular has provided objective evidence contrary to frequent insinuations and anecdotal contentions that substandard first-line HIV/AIDS medicines are present in Lusaka District.

RECOMMADATIONS

- Pharmaceutical Regulatory Authority, Ministry of Health should decentralize its laboratory operations items of GPHF Mini Lab services because this will be an effective way of complimenting the services of a newly established medium size laboratory which is centrally based in Lusaka. GPHF Mini Lab remains an indispensable tool for analysis of drugs in resource limited settings like ours.
- Pharmaceutical Regulatory Authority, Ministry of Health should recruit skilled laboratory analysts in all the nine provinces of Zambia, so that the portable GPHF Mini Lab can be utilized for routine check-ups on the quality of ARV-drugs in Zambia.
- Future research studies should be done on a larger scale to include all ARV-drugs with the help of all stakeholders, so as to have a more representative and conclusive picture on the quality of all the HIV/AIDS medicines that are available in Zambia.
STUDY LIMITATIONS

• Not all the first-line HIV/AIDS medicines were sampled and analyzed in Lusaka District partly due to:
  (i) Non-availability of reference standards at PRA as well as the manufacturers of ARVs
  (ii) High cost of some reference standards from manufacturers
  (iii) Limited number of ARVs that can be analyzed by using the GPHF Mini Lab protocols.

• High Performance Liquid Chromatography was not done to allow for further verification and possible reasons as to why some drugs were of poor quality. This is because this demands for extra financial resources and more time than is possible for masters program.

• This study did not consider the factors affecting the quality of the ARV-drugs such as manufacturing errors, transit conditions, and storage conditions and Good Manufacturing Practice (GMP) to mention but a few. The researcher is cognizant of the fact that any of these stated factors could have contributed to or be the reason for the less percentage content of NVP in sample 3A.
REFERENCES


Layloff T (2006) Drug manufacture, industrial pharmacy considerations,


UNAIDS (2008), Uniting the World against AIDS: Sub-Saharan Africa.


## ANNEXES

### Annex I: Gantt chart

<table>
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<tr>
<th>Description of activity</th>
<th>Year: 2010</th>
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<td>Research proposal</td>
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<tr>
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<tr>
<td>Data collection</td>
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<tr>
<td>Data analysis</td>
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<tr>
<td>Research report writing &amp; Submission</td>
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</table>
Annex II: Drug Information Collection Sheets

Data Collection Sheet 1


<table>
<thead>
<tr>
<th>Drug information</th>
<th>Particulars</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Name indicated on the product package</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Active ingredient(s) contained in the product as indicated on the packaging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Physical appearance of tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Nature and material of packaging material</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Appearance of the label on the packaging</td>
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<td></td>
</tr>
<tr>
<td>6. Instructions on the label for the use of the product</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Manufacturing date as stated on the product label</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Batch number of the product as stated on the label</td>
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</tr>
<tr>
<td>9. Manufacturer of the product and address as stated on the label</td>
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</table>
### Data Collection Sheet 2

<table>
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<tr>
<th>Name/ Strength</th>
<th>Batch/Lot Number</th>
<th>Manufacturer</th>
<th>Man. Date</th>
<th>Expiry date</th>
<th>Collected From</th>
<th>Quantity</th>
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<tr>
<td>Duovir</td>
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<tr>
<td>(Lamivudine/Zidovudine) Tablets 150/300mg</td>
<td></td>
<td></td>
<td></td>
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<td>60 tablets</td>
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<tr>
<td>Zidolam</td>
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<td></td>
<td>60 tablets</td>
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<tr>
<td>(Lamivudine/Zidovudine) 150/300mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>60 tablets</td>
</tr>
<tr>
<td>Zidolam</td>
<td></td>
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<td>60 tablets</td>
</tr>
<tr>
<td>(Lamivudine/Zidovudine) 150/300mg</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>60 tablets</td>
</tr>
<tr>
<td>Lamivudine/Zidovudine 150/300mg</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>60 tablets</td>
</tr>
<tr>
<td>Efavirenz Tablets 600mg</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>30 tablets</td>
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<tr>
<td>Efavirenz Tablets 600mg</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>30 tablets</td>
</tr>
<tr>
<td>Nevipam (Nevirapine) Tablets 200mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60 tablets</td>
</tr>
<tr>
<td>Nevirapine Tablets 200mg</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>60 tablets</td>
</tr>
<tr>
<td>Nevilast-30 (Lamivudine/Stavudine/Nevirapine) tablets 150/30/200mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60 tablets</td>
</tr>
<tr>
<td>Lamivudine/Stavudine/Nevirapine Tablets 150/30/200mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60 tablets</td>
</tr>
<tr>
<td>Stavudine/Lamivudine Tablets 30/150mg</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>60 tablets</td>
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Annex III: Synopsis of Chromatographic Working Conditions

The table below presents all chromatographic working conditions ARV drug compounds at a glance. For the full experimental procedure for each ARV analyzed refer to a Concise Quality Guide on ARVS of PRA, Ministry of Health of Zambia. It is accessible online: [www.gphf.org](http://www.gphf.org).

<table>
<thead>
<tr>
<th>Drug Substance</th>
<th>Final Working Concentration</th>
<th>Extraction Medium</th>
<th>Mobile Phase</th>
<th>Method of detection</th>
</tr>
</thead>
</table>
| Lamivudine     | 1.25 mg/ml                 | Water             | 11.0 ml of ethylacetate  
5.0 ml of methanol  
4.0 ml of toluene  | UV of 254 nm  
Iodine staining |
| Nevirapine     | 1.25 mg/ml                 | Acidified Water of pH 3 and below | 11.0 ml of ethylacetate  
5.0 ml of methanol  
4.0 ml of toluene  | UV of 254 nm  
Iodine staining |
| Stavudine      | 1.25 mg/ml                 | Water             | 11.0 ml of ethylacetate  
5.0 ml of methanol  
4.0 ml of toluene  | UV of 254 nm  
Iodine staining |
| Zidivudine     | 1.25 mg/ml                 | Water             | 11.0 ml of ethylacetate  
5.0 ml of methanol  
4.0 ml of toluene  | UV of 254 nm  
Iodine staining |
| Efaviranz      | 1.25 mg/ml                 | Water             | 11.0 ml of ethylacetate  
5.0 ml of methanol  
4.0 ml of acetonitrile | UV of 254 nm  
Iodine staining |

Summary of chromatographic working conditions employed in the current investigations on essential antiretrovirals. Merck TLC plates pre-coated with silica gel 60 F254 may be used as phase in all cases. Spotting volume is 2 microliters each.
 Annex IV: LABELING OF MEDICINES BASED ON STATUTORY INSTRUMENT No. 47 OF 1993

It is important to note that all medicines approved for placement on the Zambian market are required to comply with labeling requirements as stipulated in the Statutory Instrument No. 47 of 1993. It suffices to say that any deviation from this statutory requirement may be deemed to suggest that the product in question is an imitation or fake and therefore subject to questionable quality, safety, and efficacy (MoH, Register of Licensed Medicinal Products 2010).

 **Labeling of Medicines**

(1) Every package or container of medicine shall be labeled to show-
   
   (a) The name of the medicine;
   (b) The pharmacological properties;
   (c) The names and quantities of active ingredients;
   (d) The quality of the medicine;
   (e) The direction for use;
   (f) The contraindications, warnings and precautions;
   (g) The storage instructions;
   (h) The expiry date;
   (i) The batch number;
   (j) The date of manufacture;
   (k) The licence number;
   (l) The name and address of the manufacture;
   
   (m) The method of sale, that is to say, if it is to be by:

   (i) Prescription only;
   (ii) Pharmacy sale only; or
   (iii) General sale.

(2) When the space on the container of medicine is not adequate to accommodate the information specified in sub-paragraph (1), the container should be labeled to indicate the particulars (a), (c), (d), (h) and (m) of sub-paragraph (l):

Provided that the particulars specified under paragraph (b), (e), (f), (g), (i), (j), (k) and (l) of sub-paragraph (1) shall be set out on the package.
(3) Where the container of medicine is in the form of a blister or strip packet, the container shall be labeled to indicate the particulars specified in paragraphs (a) and (m) of sub-paragraph (1) and the other particulars specified in that sub-paragraph shall be set out on the package.

(4) The provisions of this paragraph shall not apply to dispensed medicines:

(5) Every package or container of dispensed medicine shall be labeled to indicate-
   (a) The name of the person to whom the medicine is to be administered;
   (b) The dosage or where the medicine is to be used;
   (c) The date on which the medicine is dispensed; and
   (d) Any other information necessary to ensure the correct use of the medicine.

(6) A package or container of dispensed medicine may indicate the name and address of suppliers of the medicine.

(7) Where a package or container of dispensed medicine is to be administered to an animal, the package or container shall be labeled to indicate-
   (a) The name and address of the person in control of the animal;
   (b) Name and address of the suppliers of medicine;
   (c) The date on which the medicine is dispensed; and
   (d) Any other information necessary to ensure the correct use of the medicine.
31st January, 2010

The above mentioned person is a bonafide student of the University of Zambia, Department of Community Medicine pursuing a Masters Degree in Public Health.

He is requesting for permission to collect 215 tablets/capsules of first-line ARVs for his research project from ten Private Health Institutions in Lusaka. He is expected to sample only 22 tablets/capsules from each Institution.

I further request your esteemed office to permit him use your Minilab facilities to analyze the samples of Antiretroviral drugs in order to verify the quality of the drug samples for his study entitled “QUALITY ANALYSIS OF FIRST-LINE HIV/AIDS MEDICINES DISPENSED IN LUSAKA URBAN DISTRICT HEALTH FACILITIES OF ZAMBIA”

Your assistance will be highly appreciated.

Yours faithfully,

Dr. S. H. Nzala
MPH COORDINATOR
Dear Madam/Sir

RE: REQUEST FOR MUNKOMBWE DERICK TO COLLECT DRUG SAMPLES FROM GOVERNMENT INSTITUTIONS IN LUSAKA.

The above mentioned person is a bonafide student of the University of Zambia, Department of Community Medicine pursuing a Masters Degree in Public Health.

He is requesting for permission to collect 215 tablets/capsules of first-line antiretroviral drugs (ARVs) for his research project from ten PUBLIC Health Institutions in Lusaka. He is expected to sample only 22 tablets/capsules of ARVs from each Institution.

He will be analyzing these samples in order to verify the quality of ARVs dispensed in Lusaka. His study title is “QUALITY ANALYSIS OF FIRST-LINE HIV/AIDS MEDICINES DISPENSED IN LUSAKA URBAN DISTRICT HEALTH FACILITIES OF ZAMBIA”

Your assistance will be highly appreciated.

Yours faithfully,

Dr. S.H. Nzala
MPH COORDINATOR
Annex VII: Ethics Approval Letter

THE UNIVERSITY OF ZAMBIA

BIOMEDICAL RESEARCH ETHICS COMMITTEE

Telephone: 260-1-256067
Telegrams: UNZA, LUSAKA
Telex: UNZA1UZA 44370
Fax: 260-1-258075
Email: unzrorc@unza.zm

Assurance No. FWA00000338
IRB00001131 of IORG0000774

22 June, 2010
Ref. 024-06-10

Mr Derrick Munkombwe
Department of Community Medicine
UNZA School of Medicine
P.O. Box 50110
LUSAKA

Dear Mr Munkombwe,

RE: SUBMITTED RESEARCH PROPOSAL: “QUALITY ANALYSIS OF FIRST-LINE HIV/AIDS MEDICINES DISPENSED IN LUSAKA URBAN DISTRICT HEALTH FACILITIES OF ZAMBIA”

The above-mentioned research proposal was presented to the Biomedical Research Ethics Committee on 7 June, 2010 where changes/clarifications were recommended. We would like to acknowledge receipt of the corrected version with clarifications. The proposal is now approved.

CONDITIONS:

• This approval is based strictly on your submitted proposal. Should there be need for you to modify or change the study design or methodology, you will need to seek clearance from the Research Ethics Committee.
• If you have need for further clarification please consult this office. Please note that it is mandatory that you submit a detailed progress report of your study to this Committee every six months and a final copy of your report at the end of the study.
• Any serious adverse events must be reported at once to this Committee.
• Please note that when your approval expires you may need to request for renewal. The request should be accompanied by a Progress Report (Progress Report Forms can be obtained from the Secretariat).
• Ensure that a final copy of the results is submitted to this Committee.

Yours sincerely,

[Signature]

Dr James Muntalili
Chairperson

Date of approval: 22 June, 2010
Date of expiry: 21 June, 2011
THE UNIVERSITY OF ZAMBIA  
SCHOOL OF MEDICINE

06th April, 2010

Mr Derrick Munkombwe  
Department of Community Medicine  
LUSAKA

Dear Mr Munkombwe,

RE: GRADUATES PROPOSAL PRESENTATION FORUM (GPPF)

Having assessed your dissertation entitled “Quality Analysis of First Line HIV/AIDS Medicines Dispensed in Lusaka Urban District Health Facilities of Zambia”. We are satisfied that all the corrections to your research proposal have been done. The proposal meets the standard as laid down by the Board of Graduate Studies.

You can proceed and present to the Research Ethics.

Yours faithfully,

Mr. K. Bowa, MSc, M.Med, FRCS, FACS, FCS (UroI)  
ASSISTANT DEAN, POSTGRADUATE

CC: Head of Department – Community Medicine
23rd July 2010

Mr Derrick Munkombwe
Department of Community Medicine
UNZA School of Medicine
P.O Box 50110
LUSAKA

Dear Mr Munkombwe,

Re: Request for Authority to Conduct Research

We are in receipt of a request for authority to conduct a study on “The Quality Analysis of First-line HIV/AIDS Medicines Dispensed in Lusaka Urban District Health Facilities of Zambia”. I wish to inform you that following submission of your research proposal to my Ministry, our review of the same, my Ministry has granted you authority to carry out the study on condition that:

1. The relevant Provincial and District Directors of Health where the study is being conducted are fully appraised;
2. Progress updates are provided to MoH quarterly from the date of commencement of the study;
3. The final study report is cleared by the MoH before any publication or dissemination within or outside the country.

This study is of policy relevance in HIV/AIDS programmes.

Yours sincerely,

[Signature]
Dr. P. Mwaba
Permanent Secretary
MINISTRY OF HEALTH

c.c. Director Public Health and Research

c.c. Provincial Medical Officer - Lusaka
Annex X: Lusaka District Health Management Team Approval Letter

27 August 2010

Mr Derrick Munkombwe
Department of Community Medicine
UNZA School of Medicine
P O Box 50110
LUSAKA

Dear Mr. Munkombwe

RE: THE QUALITY ANALYSIS OF FIRST-LINE HIV/AIDS MEDICINES DISPENSED IN LUSAKA DISTRICT HEALTH FACILITIES OF ZAMBIA

We are in receipt of your letter over the above subject.

We have since received the letter of authority for the above study from the Ministry of Health and therefore, Lusaka DHMT has no objection for you to collect the drug samples from Bauleni, Chelstone, Kabwata, Kalingalinga, Kamwala, Kanyama, Makeni, Matero Main, and Mtendere health centres.

By copy of this letter the respective Health Centre In-charges are herewith informed.

Please ensure that a copy of the summary of findings is also provided to LDHMT at the end of the research study.

Yours faithfully,

DR. C. MBWILI-MULEYA
AG/DISTRICT MEDICAL OFFICER

CC: In-charge – Bauleni, Chelstone, Kabwata, Kalingalinga, Kamwala, Kanyama, Makeni, Matero main and Mtendere health centres
Annex XI: Quotation for ARV Reference Standards

**LGC Standards**
*Excellence through measurement*

---

**Commercial Invoice**

**Consignee Address**
Tejay Pharmaceuticals Ltd  
Plot 12147, Off Mumbwa Road,  
Chinika Industrial Area  
- Lusaka  
P.O. Box 34315  
ZM - ZAMBIA

**Invoice Address**
Tejay Pharmaceuticals Ltd  
Plot 12147, Off Mumbwa Road,  
Chinika Industrial Area  
- Lusaka  
P.O. Box 34315  
ZM - ZAMBIA

Contact: Cosmos Banda  
Email: bandacosmas@yahoo.com

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**SUBTOTAL**  
567.15  
60.00

**Freight Charges**  
627.15

**Total Value Including Shipping**  
627.15

**Sender Contact Details**
Ms Nicola Shaw  
Email: uksales@lgcstandards.com  
Tel: 0208 943 7682

**Shipment Data**
Despatch by: Preferred Method  
Delivery: DOU, Lusaka  
Payment: Due Immediately

---

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