

## **CHAPTER 1**

### **1.0 INTRODUCTION**

The Government of the Republic of Zambia is committed to improving the quality of life for all Zambians, and this commitment is demonstrated through the government's efforts to improve health care delivery by reforming the health sector. In 1991, the Government of the Republic of Zambia launched radical health policy reforms characterized by a move from a strongly centralized health system in which the central structures provided support and national guidance to the peripheral structures. An important component of health policy reform is the restructured Primary Health Care (PHC) programme. The government is committed to providing efficient and cost-effective quality basic health care services for common illnesses as close to the family as possible through the implementation of the Basic Health Care Package (BHCP) at all levels of health care (ZDHS.2007). Currently, the following priority areas for health services have been identified for inclusion into the basic health care package: nutrition; environmental health, control and management of communicable diseases such as malaria, tuberculosis, epidemic and disaster prevention, preparedness and response, school health, and oral health (MoH strategic plan. 2006 - 20011).

At the global level, the importance of tuberculosis and its association with the HIV/AIDS pandemic are acknowledged by the Millennium Development Goals, and unprecedented funds are being provided by the Global Fund to fight HIV/AIDS, Tuberculosis, and Malaria. Zambia has joined the rest of the world in striving to attain the Millennium Development Goals (MGDs) in response to the world's main development challenges. Of much concern to this study is Goal Number 6 which aims at combating HIV/AIDS,

Malaria and TB. Combating the above mentioned communicable diseases will require the use of quality, safe and efficacious drugs. In recognition of the dangers and consequences of using counterfeit and substandard drugs, and the threat this poses to public health, the Government of the Republic of Zambia established the Pharmaceutical Regulatory Authority in 2006 to strengthen Pharmaceutical regulation in the country.

Fixed dose combination (FDC) anti TB drugs used in Zambia come as imports from other countries because the few local pharmaceutical manufacturing companies can not manufacture anti TB drugs. Access to these drugs is through the public institutions such as the Government run hospitals and clinics, the private institutions (hospitals and clinics). What is of much concern is the quality of the drugs used by the people of Zambia as there is inadequate post – marketing surveillances on these drugs. The consequence of using counterfeit and substandard FDC drugs is a high burden of the disease leading to increased adverse effects, multi drug resistance tuberculosis, high mortality and morbidity.

Drug quality is currently receiving renewed international attention. Over the past decade, there has been an increase in public awareness of the existence of counterfeit and substandard drugs, which have been increasingly reported in developing countries where drug regulations are ineffective. Many factors contribute to the increased prevalence of substandard and counterfeit medications such as chemical instability especially in tropical climates, and poor quality control during manufacture. Much of the counterfeit drug trade is probably linked to organized crime, corruption, the business interests of unscrupulous politicians and unregulated pharmaceutical companies (WHO,1999).

The aim of the study was to evaluate the quality of fixed dose combination anti TB drugs in Lusaka district so as to find ways of strengthening the fight against the use of drugs in general, and also contribute to the fight against the spread of multi drug resistance TB that has complicated treatment outcomes in other parts of sub-Saharan Africa and the world at large.

## **1.1 BACKGROUND**

Tuberculosis is a major public health problem in Zambia. It is an airborne infectious disease which is caused by mycobacterium tuberculosis and primarily affects the lungs but can also affect other tissues of the body. The disease is chronic in nature with varying clinical manifestations and can only occur when the health of an individual is compromised. The mycobacterium causative agent was discovered more than 100 years ago and highly effective drugs and vaccines are available making tuberculosis a preventable and curable disease (Park. 2007). TB prevention programs and treatment packages including DOTs have been applied over the years in Zambia. TB cure rate of 72.5% in 2003 was achieved in the reported cases of active TB, but this is not enough to provide an environment which can render TB not a public health problem (MOH. 2006c).

Because of the magnitude of the TB problem that has also been acknowledged by WHO that declared Tuberculosis a global emergency in 1993, it is imperative that concerted efforts are made aimed at ensuring that strategies used to reduce the incidence of the disease are working. Apart from the DOTs strategy, the quality of anti TB drugs being used must be of acceptable quality. However, this is being compounded by many reports of substandard and counterfeit anti TB drugs on the global market (Laserson et al: 2001).

The production of substandard and fake drugs is a vast and underreported problem, particularly affecting poorer countries. It is an important cause of unnecessary morbidity, mortality, and loss of public confidence in medicines and health structures. The prevalence of substandard or counterfeit drugs appears to be rising. For instance, it has been estimated that up to 15% of all sold drugs are fake, and in some parts of Africa and Asia the figure exceeds 50% (Robert et al: 2007).

Substandard or counterfeit medicines represent an enormous public health challenge. These drugs come in the form of tablets or capsules that look right, but do not contain the correct ingredients and, in the worst case scenario, may be filled with inactive, useless preparations or highly toxic substances. In some countries, this is a rare occurrence while in others, it is common. In all cases, contents of counterfeits are unreliable because their source is unknown or vague and always illegal. Fake drugs can cause harm and sometimes lead to death (WHO, 2006).

According to WHO, 2006 Counterfeit (fake) drugs are products deliberately made to resemble a brand named pharmaceutical. They may contain no active ingredient or contain ingredients inconsistent with the package description. Substandard drugs are found even among cheaper products, and are also common among more expensive drugs, because some manufacturers wish to avoid costly quality control and good manufacturing practices.

The quality of commercially available drugs varies greatly among countries. Due to lack of regulations and poor quality control practices in some countries especially developing countries, the amount of active ingredients can be inconsistent. or formulation techniques can affect the release of active ingredients from a tablet, with some tablets releasing very little active ingredient. Some drugs may be contaminated with other substances. Poor storage conditions,

especially in warm and humid tropical environment may contribute to chemical degradation of many pharmaceuticals. However, according to Ashokraj et al (2005), Angrawal et al (2004) and Theodore et al (2007), in contrast to other medications, anti-TB drugs are stable under storage conditions, so that substandard levels are usually not caused by instability but by a lack of adherence to standard good manufacturing practices (GMP).

## **1.2 QUALITY, SAFETY AND EFFICACY OF DRUGS**

Poor quality medicines do not meet official standards for strength, quality, purity, packaging and labeling. They may be legally registered innovator or generic products, or they could be counterfeits—deliberately mislabeled for identity, strength, or source. The quality of pharmaceuticals is a global concern, and the lack of reliable drug quality assurance systems in many developing countries often contribute to the devastation of diseases, particularly those that have built up resistance to traditional first-line medicines (United States Pharmacopoeia, 2008).

The safety of medicines is an essential part of patient safety. Global drug safety depends on strong national systems that monitor the development and quality of medicines, report their harmful effects, and provide accurate information for public use. Harmful, unintended reactions to the medicines that occur at doses normally used for treatment are called adverse drug reactions (ADRS). ADRS are among the leading causes of death in many countries. Global information-sharing on the adverse effects strengthens drug safety in countries, and can translate into timely policy decisions that safeguard patient safety when problems emerge (WHO, 2008).

Efficacy of drug is the capacity of the drug to produce an effect. It indicates the capacity for beneficial change or a therapeutic effect (Merck, 2007). A therapeutic effect is a consequence of a medical treatment of any kind, the results of which are judged to be desirable and beneficial.

Therefore, drug efficacy refers to the potential maximum therapeutic response that a drug can produce.

### **1.3 STATEMENT OF THE PROBLEM**

Apart from struggling with the burden of communicable diseases and transitioning to non communicable diseases, developing countries such as Zambia are also faced with the challenge of the availability of Counterfeit and substandard medicines on their markets which are an insidious threat to global health and the risks they pose have been largely underestimated to date. Apart from failing to cure disease, counterfeit and substandard drugs can cause mental and physical damage and even death. Counterfeit and substandard drugs containing insufficient active ingredients breed resistance, which can make standard drugs useless. (Bate and Boateng, 2007).

Almost all areas of the world are affected by the availability of substandard and counterfeit medicines, but mounting evidence shows that the problem is disproportionately severe in developing and emerging market countries, which also have a high burden of infectious diseases. In poor countries, essential and life-saving drugs used to treat infectious diseases such as tuberculosis and malaria are often the drugs under threat (Bate and Boateng, 2007). Counterfeit and substandard medicines present an enormous public health challenge. They range from random mixtures of harmful toxic substances to inactive, useless preparations (WHO, 2006).

According to WHO, 2006), Substandard drugs do not meet official standards for strength, quality, purity and / or labeling, and these drugs result in serious health implications such as

- (a) Lacking therapeutic effect and causing treatment failure,
- (b) Severe adverse effects,

- (c) Increased morbidity and mortality,
- (d) Development of drug resistance and in the case of Tuberculosis Multi Drug Resistance Tuberculosis
- (e) Waste of resources.

As from the above statements it is quite clear that the problem of counterfeit and substandard anti TB drugs is a growing threat to global health and has not spared Sub Saharan Africa as shown by studies conducted in South Africa and Botswana (Pillai et al, 1999, Kenyon et al, 1999). In Zambia there is almost complete absence of both qualitative and quantitative published data that is recent on the prevalence of counterfeit and substandard fixed dose combination (FDC) anti Tuberculosis drugs. Whereas the FDC anti TB drugs that are used in government institutions may be subjected to quality control analysis using the PRA minilab, those used in private hospitals and clinics may not. To try and address this problem the Ministry of Health has partnered with private hospitals whereby these hospitals are given drugs by the Ministry so that patients can still access free TB treatment in the private hospitals. However, due to inadequate post-marketing surveillance on Pharmaceuticals in the country, there is need to try and quantify the problem of substandard drugs and counterfeits if any corrective measures are to be put in place.

Factors that have been suggested by WHO (2006) to contribute to the production and sale of counterfeit and 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.
- Corruption and conflict of interest.

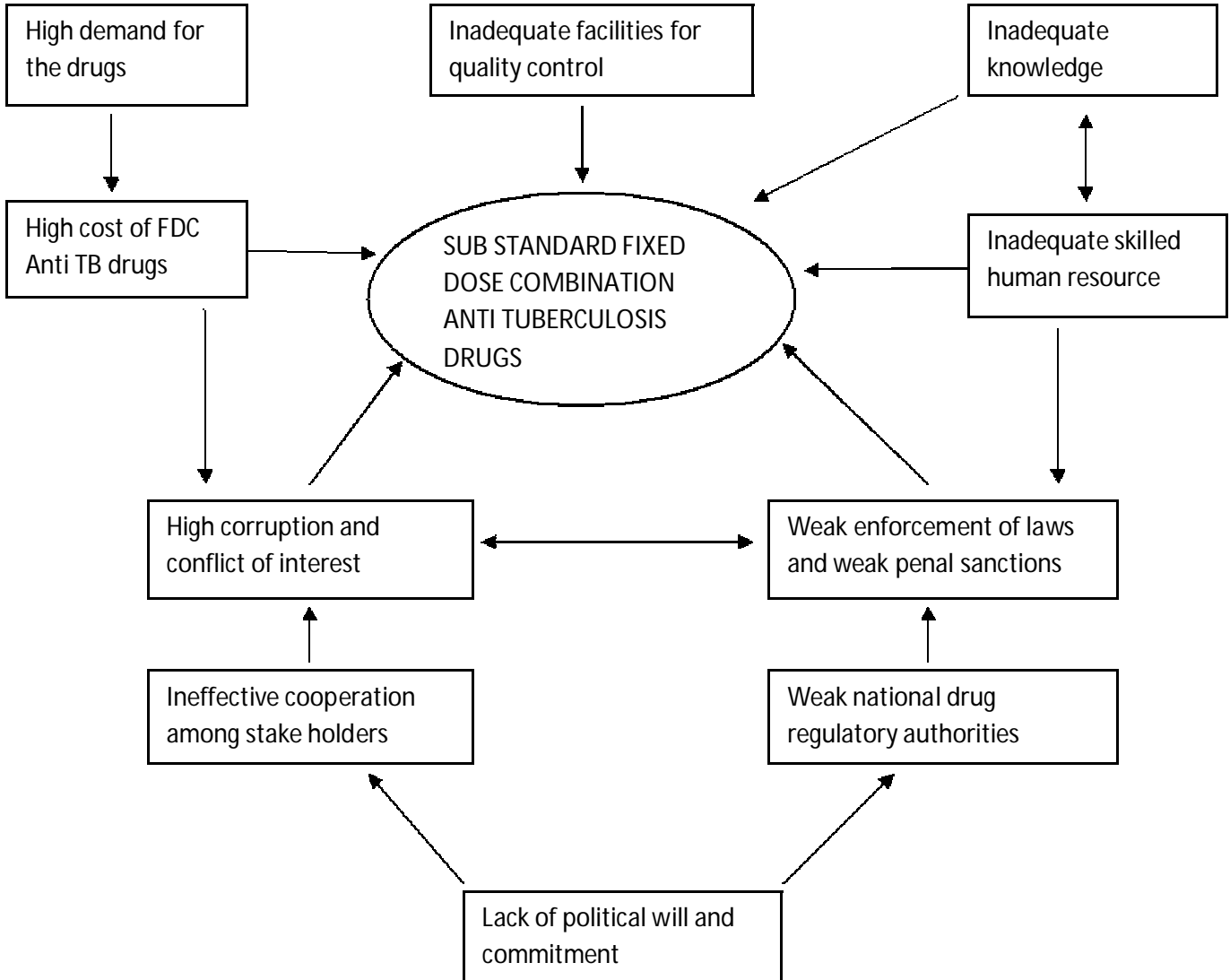
#### **1.4 RATIONALE OF THE STUDY**

The rationale of the study was to evaluate the quality of fixed dose combination anti TB drugs in Lusaka district so as to find ways of strengthening the fight against  ing of drugs in general, and also contribute to the fight against the  of multi drug resistance TB that has complicated treatment outcomes in other parts of sub-Saharan Africa and the world at large.

This study also aimed to generate information that would help to maximize the effectiveness of tuberculosis control efforts currently being undertaken in Zambia by bringing out information on the quality of fixed dose combination (FDC) anti TB drugs being used and the information generated would also add to the body of knowledge on the TB control efforts in Lusaka District and the country as a whole.



**1.5 PROBLEM ANALYSIS DIAGRAM:**



## **1.6 RESEARCH QUESTION**

Did the quality of the available fixed dose combination (FDC) anti TB drugs in public and private health facilities in Lusaka District meet the required standard as prescribed in the official monographs.

## **1.7 STUDY OBJECTIVES.**

### **1.7.1 GENERAL OBJECTIVE:**

To determine the quality of fixed dose combination (FDC) anti TB drugs, 4FDC- (Rifampicin / Isoniazid / Pyrazinamide / Ethambutol, 3FDC - (Rifampicin / isoniazid / Pyrazinamide) and Rifinah - (Rifampicin / Isoniazid) tablets available in Lusaka District.

### **1.7.2 SPECIFIC OBJECTIVES:**

1. To verify the active ingredients contained in the collected samples of (4FDC) – (Rifampicin / Isoniazid / Pyrazinamide / Ethambutol), (3FDC) - Rifampicin / isoniazid / Pyrazinamide and (Rifinah) - Rifampicin / Isoniazid with reference to the label claim using Spectrophotometry.
2. To determine the percentage content of the active ingredients in the FDC anti TB drugs that were sampled and analyzed.
3. To assess the packaging and labeling on the packaging of the collected samples of Rifampicin / Isoniazid / Pyrazinamide / Ethambutol (4FDC), Rifampicin / Isoniazid / Pyrazinamide (3FDC) and Rifampicin / Isoniazid (Rifinah) with reference to pharmaceutical standard reference books.

4. To ascertain the proportions of (4FDC) - Rifampicin / Isoniazid / Pyrazinamide / Ethambutol, (3FDC) - Rifampicin / isoniazid / Pyrazinamide and (Rifinah) - Rifampicin / Isoniazid from the collected samples which are substandard and counterfeit.

## **1.8 STUDY VARIABLES**

### **1.8.1 Dependant variables**

- Substandard drugs

### **1.8.2 Independent variables**

- Active ingredients
- Percentage content of active ingredient
- Labeling
- Packaging

## **CHAPTER 2**

### **2.0 LITERATURE REVIEW**

Tuberculosis (TB) continues to be a major health threat in Zambia and is ranked among the top 10 causes of morbidity and mortality. Zambia has one of the highest incidence rates of TB per capita in the world. The sputum-smear positive (SS+) case notification rate in Zambia is 193 cases per 100,000 population, more than three times the global average of 61 cases per 100,000 population. Zambia also has the 10<sup>th</sup> highest incidence rate in the world (ZDHS, 2007).

In Zambia, TB also accounts for about one out of every six adult deaths in health facilities and about 100,000 Zambians have active TB. It is a notifiable disease which can easily or quickly spread within a population causing high morbidity and mortality (MOH, 2005). It is also important to highlight that one third or more of Zambians carry TB bacteria in their bodies, but it is inactive until immunity is compromised. HIV/AIDS is one of the diseases which can reduce someone's immunity (MOH, 2006a).

Over the years TB notification (TB disease) has been increasing and this is of concern because of its impact on patients, their families and government through spending on diagnosis and treatment, transport to get to the health facility and time lost from work. This scenario affects the quality of life of an individual, families and communities as well as the economic development of the nation.

The number of TB notifications increased from 5,321 in 1980 to 53,267 in 2005 and was highest in 2004 with 58,070. This is an obvious indication that the disease is on the increase and calls for concerted efforts other than the diagnosis and curative approach by Ministry of Health. TB mostly affects a prime age group of 20 to 35 years which is a productive age group. A single set

back in this group will affect the national development and social stability in the country. The annual risk infection rate in Zambia is estimated to be around 2.5% (MOH, 2005) which is well above the international infection rate of 1.8% making it a national emergency. Looking at the age group affected, it is therefore important that approaches to contain and prevent the spread of the disease are explored and these approaches should include among other things looking at the quality of anti TB drugs that patients are given for treatment. WHO declared the disease a global emergency in 1993 while Africa ministers of health declared TB a regional emergency in 2005 in Maputo, Mozambique (MOH, 2005).

## **2.1 GLOBAL PERSPECTIVE**

Substandard drug preparations are present throughout the world. Despite the potential contribution of poor quality drugs to the creation of drug resistant Mycobacterium Tuberculosis organisms, the global prevalence of substandard anti TB drugs has not been systematically assessed (Laserson et al, 2001). A study that involved the screening of single and fixed dose combination (FDC) anti TB drugs from selected TB programs from Colombia, Estonia, India, Latvia, Russia and Vietnam was done using a method called Thin Layer Chromatography (TLC). The results from this study showed that a substantial percentage of anti Tuberculosis drugs from several countries, in particular FDC were found to be substandard. 10% (4/40) of all samples contained less than 85% of stated content, 13% (4/30) rifampicin samples contained less than 85% of stated content. The study also showed that more FDCs (5/24, 21%) than single drug samples (2/16, 13%) were substandard. Such drugs may contribute to the creation of drug resistant Tuberculosis. (Laserson et al, 2001).

## **2.2 REGIONAL PERSPECTIVE**

The problem of substandard drugs has not spared Africa and the Southern African region in particular. Studies done in three countries confirmed existence of substandard FDC anti TB drugs in these countries where the studies were conducted.

In 2001 a study was done in Nigeria to check the quantity of active ingredients in anti TB drugs and the results showed that more than 50% of the Anti TB drugs failed to comply with the official monographs. The tested drugs had low quantities of the active ingredients (Taylor et al, 2001).

In 1999, a study was also conducted in South Africa that involved screening of FDC formulations and the results showed that 70% (7/10) of the samples had Rifampicin being non bioequivalent to the official monograph and this had serious implications on treatment outcomes for TB hence the moderately high rate of multi drug resistance (MDR) cases that were recorded in the country (Pillai et al, 1999).

Another study was done in Botswana in 1999 that involved quantitative analysis of 13 FDC anti TB samples and the results obtained showed that 31% (4/13) of the samples were substandard with 15% (2/13) having less than 85% Rifampicin as active ingredient, 8% (1/13) having more than 115% of Rifampicin and 8% (1/13) of the samples having more than 115% Pyrazinamide. The gold standard used was Ultra Violet Spectrophotometry with a sensitivity of 100% and specificity of 90% (Kenyon et al, 1999).

### **2.3 NATIONAL PERSPECTIVE**

There is no documented evidence about any research done to determine the existence of substandard FDC anti TB drugs in Zambia. However, the Government of the Republic of Zambia has shown its commitment to fight the scourge by establishing institutions such as the Pharmaceutical Regulatory Authority (PRA) and the Drug Enforcement Commission (DEC). Furthermore, on 11<sup>th</sup> November 2008, the government formed the Drug Taskforce to fight counterfeiting of drugs in the country.

It is also important to note that there is no recent published data on studies that have been conducted on substandard and counterfeit fixed dose combination (FDC) anti TB drugs and the available data was published in 1999, 2001 and 2002 respectively (Laserson et al, 2001, WHO. 2003).



## **CHAPTER 3**

### **3.0 RESEARCH METHODOLOGY**

#### **3.1 STUDY SETTING`**

The study was undertaken in Lusaka District because TB drugs that are ordered into the country by the Ministry of Health courtesy of cooperating partners and other private pharmaceutical companies are stored in Lusaka before distribution to treatment through out the country. Most of the pharmaceutical businesses in Zambia are also concentrated in this district, and this made it easy to collect drug samples to be analyzed. The analysis of fixed dose combination (FDC) anti TB drugs was done at Tejay Pharmaceuticals Laboratory situated in Lusaka.

#### **3.2 STUDY POPULATION**

The study population included seventeen fixed dose combination anti TB drugs collected from both government and private health institutions offering TB treatment services in Lusaka District. These comprised five 4FDC samples, five 3FDC samples and seven samples of Rifinah. The drug samples from all these places with different batch numbers were selected using simple random sampling taking note of the batch numbers in order to avoid duplication of drug samples.

#### **3.3 STUDY DESIGN**

This was a cross sectional study and the following parameters were considered:

1. Appearance of the tablets
2. Labeling on the packaging materials
3. Type of packaging material
4. Presence of active ingredient in the samples

5. Percentage content of the active ingredients (this should fall between 95% and 105% for Ethambutol, Pyrazinamide and Isoniazid and 92.5% to 107.5% for Rifampicin as indicated in the official monograph (BP, 2008).

### **3.4 INCLUSION CRITERIA**

All FDC anti TB tablets available in the sampled facilities in Lusaka District were included in the study, as long as they were not expired with reference to the expiry date on the label, and that their shelf- life was not less than twelve months at the time of the study.

### **3.5 EXCLUSION CRITERIA**

Non fixed dose combination (non FDC) and fixed dose combination (FDC) anti TB drugs that were expired or had less than twelve months shelf- life were not included in the study.

### **3.6 SAMPLING METHODS**

A systematic sampling method was used to sample the facilities and simple random sampling was used to sample the tablets.

### **3.7 SAMPLE SIZE DETERMINATION**

The following formula was used to calculate the number of tablets that was collected for analysis.

$$N = Z^2 P (100-P)/d^2$$

Where;  $Z = 1.96$ , factor from normal distribution

$P =$  Expected period prevalence - (50)

$d =$  Absolute sampling error

$n =$  Sample size

The study aimed to tolerate an absolute sampling error of up to 5%, with power of the study at 95%.

Therefore  $n = \frac{(1.96)^2 \times 50(100 - 50)}{52}$

= 384 tablets, add 10% handling loss

= 422 rounded off to 430

So 430 tablets were required for the study but 58 tablets were collected for each sample and a total of 952 tablets were collected for the research.

### **3.8 DATA COLLECTION TOOLS**

A drug collection sheet, which provided information on the date, place, and conditions of the tablets, the name of the drug as indicated by the seller and the name stated on the product label as well as the active ingredient indicated on the label was used.

### **3.9 DATA COLLECTION TECHNIQUES**

Drug samples that were obtained with permission from the Permanent Secretary, Ministry of Health and the District Medical Officer for Lusaka district health office were analyzed in the laboratory at Tejay Pharmaceuticals using ultra violet (UV) spectrophotometry method as well as electric titrations to get the data that in turn was used to get the values of drug content as percentages.

### **3.10 DATA QUALITY CONTROL CHECKS**

The researcher worked closely with the laboratory quality control manager at Tejay Pharmaceuticals in order to ensure that all the protocols were followed as provided for in the official monograph.

### **3.11 ETHICAL CONSIDERATIONS**

This study did not involve human subject, however, clearance was sought from the University of Zambia Biomedical Research Ethics Committee (UNZA BREC). Permission was also sought from the Permanent Secretary (MoH) for sample collection from both public and private institutions where anti tuberculosis services were provided.

### **3.12 DATA ANALYSIS**

Quantitative data was analyzed manually and this involved calculations to find the concentration of each active ingredient as percentages in each sample that was collected and then the data was entered into tables.

### 3.13 MATERIALS AND METHODS

The drugs that were used in the study were anti tuberculosis drugs that are used in the treatment of TB according to the national tuberculosis treatment guidelines for Zambia. These were all fixed dose combination drugs that were collected from points of distribution to the patients. These drugs are antibacterial and have been formulated in fixed dose combination to reduce pill burden to the patients and thereby increase compliance. Three fixed dose combination drugs were used in this study and their details are indicated in the table 3.13.1

**Table 3.13.1 Drugs used for the purpose of this study**

<b>Drug Class</b>	<b>Name of Drug</b>	<b>Drug Combination</b>	<b>Formulation</b>
Antibacterial	4FDC	Pyrazinamide Ethambutol Rifampicin Isoniazid	Tablet
Antibacterial	3FDC	Ethambutol Rifampicin Isoniazid	Tablet
Antibacterial	2FDC	Rifampicin Isoniazid	Tablet

Drug quality was assessed by measuring the level of active ingredient content as a percentage of stated content in the tablet samples in compliance to the official monograph. The acceptable levels for each drug according to the official monograph (BP 2008) are indicated in table 3.13.2

### 3.13.2. Specifications for acceptable levels of each drug according to BP. 2008

Drug	Acceptable % content in Official monograph (BP 2008)
Pyrazinamide	95 – 105%
Ethambutol	95 – 105%
Rifampicin	92.5 – 107.5%
Isoniazid	95 – 105%

The other materials used in the research are indicated in the assays for individual drugs.

#### 3.14.1 PYRAZINAMIDE

##### A. IDENTIFICATION

For each sample a quantity of powdered tablets containing 250mg of Pyrazinamide was shaken with 20ml of absolute Ethanol in a volumetric flask. This was filtered and the filtrate was then evaporated to dryness. The residue was dried at 105 degrees for 30 minutes in an oven. The infrared absorption spectrum of the residue was found to be concordant with the reference spectrum of Pyrazinamide (RS 306).

##### B. ASSAY

For each sample 20 tablets were weighed and powdered, 200ml of water was added to a quantity of the powder containing 100gm of pyrazinamide and allowed to stand for 10 minutes swirling occasionally for ten minutes and then this was diluted to 500ml with water. The solution was then filtered discarding the first 20ml of the filtrate. Then 5ml of the filtrate was diluted 100ml with water and the absorbance of the resulting solution was measured at the maximum at 268nm. The content of pyrazinamide was calculated taking 650 as the value of  $A(1\%, 1\text{cm})$  at the maximum at 268nm using the formula  $A(1\%, 1\text{cm}) = 10e/M$

### **3.14.2 ISONIAZID**

#### **A. IDENTIFICATION**

To a quantity of powdered tablets containing 100mg of Isoniazid 10ml of ethanol (95%) was added and shaken for 15 minutes. This was then put in centrifuge and the supernatant liquid was decanted. The residue was extracted further with two 10ml of ethanol (95%) and the extracts were evaporated to dryness. The infrared absorption spectrum of the residue was found to be concordant with the reference spectrum of Isoniazid (RS 196).

#### **B. ASSAY**

20 tablets of each sample were weighed and powdered separately. Then a quantity of the powder containing 400mg of Isoniazid was dissolved completely in water in a volumetric flask. This was filtered and the residue was washed with sufficient water to produce 250ml. Then to 50ml of the resulting solution 50ml of water, 20ml of hydrochloric acid and 200mg of potassium bromide were added and this was titrated with 0.016M potassium bromide Volumetric Solution (VS) and the end point was determined electrometrically. The percentage content of isoniazid was then calculated taking 1ml of 0.016M potassium bromide VS to be equivalent to 3.429mg of isoniazid. Percentage content should fall between 95% and 105%.

### **3.14.3 RIFAMPICIN**

#### **A. IDENTIFICATION**

The powdered contents of one tablet from each sample which contain 150mg of Rifampicin were shaken with 5 ml of chloroform. This was then filtered and the filtrate was evaporated to

dryness. The infrared absorption spectrum of the residue was concordant with the reference spectrum of rifampicin (RS 312).

## **B. ASSAY**

80ml of methanol was mixed with a quantity of powdered content of 20 tablets of 4FDC containing 100mg of rifampicin in a volumetric flask. Sufficient methanol was added to produce 100ml. This was then filtered and 2ml of the filtrate diluted to 100ml with phosphate buffer (pH 7.4) and the absorbance of the resulting solution was measured at the maximum at 475nm. Then the content of rifampicin was calculated taking 187 as the value of  $A(1\%, 1\text{cm})$  using the formula  $A(1\%, 1\text{cm}) = 10e/M$  (where M is the molecular weight).

### **3.14.4 ETHAMBUTOL**

#### **A. IDENTIFICATION**

A quantity of powdered tablets containing 100mg of Ethambutol Hydrochloride from each sample was shaken with 10 ml of water in a conical flask. This was filtered and 2 ml of a 1% w/v solution of Copper (II) Sulphate was then added to the filtrate followed by 1 ml of 1M Sodium Hydroxide. A blue colour was produced indicating the presence of Ethambutol.

#### **B. ASSAY**

20 ml of 2M sodium hydroxide was added to a quantity of the powdered tablets containing 200mg of Ethambutol hydrochloride and mixed for 5 minutes in a volumetric flask. A mixture of 3 volumes of chloroform and 1 volume of propan-2-ol was extracted with three successive 25 ml quantities and each extract was filtered successively through the same filter consisting of anhydrous sodium sulphate on an absorbent cotton plug moistened with a mixture of 3 volumes



of chloroform and 1 volume of propan-2-ol. The plug was washed with 10 ml of the same solvent mixture. 100 ml of anhydrous acetic acid was then added to the combined extracts and washings. Method I for non-aqueous titration was carried out using 1-naphtholbenzein solution as indicator. Each ml of 0.1M perchloric acid VS was equivalent to 13.86 mg of  $C_{10}H_{24}N_2O_2 \cdot 2HCl$ .

## CHAPTER 4

### 4.0 DATA PRESENTATION

#### 4.1 INTRODUCTION

The findings presented here are from data that was obtained through the analysis of study samples that were obtained from both government and private clinics where anti Tuberculosis services are provided. The data was obtained through laboratory analysis of samples of fixed dose combination anti tuberculosis drugs to check for presence of active ingredient as indicated on the label claim as well as percentage content of the active ingredient. Data was collected over a period of two months and presented by way of cross tabulation.

#### 4.2 ANALYTICAL RESULTS

##### 4.2 4FDC

Figure 4.2.1 shows results for the identification tests that were done on the individual drugs contained in 4FDC samples that were analyzed. All the four drugs that were contained in 4FDC tested positive to the identification tests.

**Table 4.2.1 Results of identification tests done on 4FDC samples**

Drug Code	Pyrazinamide	Ethambutol	Rifampicin	Isoniazid	Overall Result
1A	+	+	+	+	Pass
1B	+	+	+	+	Pass
1C	+	+	+	+	Pass
1D	+	+	+	+	Pass
1E	+	+	+	+	Pass

*+= Positive identification test*

Table 4.2.2 shows absorbance values for Pyrazinamide and Rifampicin and titrated volumes of Perchloric acid for Ethambutol and Potassium bromide for Isoniazid respectively. The table also shows the calculated drug content values for individual drugs that constituted the 4FDC drug samples.

**Table 4.2.2 Drug content values for the four drugs in 4FDC drug samples**

Drug Code	Mean Tablet Weight (mg)	Pyrazinamide		Ethambutol		Rifampicin		Isoniazid	
		Drug content (mg)	(A)	Drug content (mg)	Volume (ml)	Drug content (mg)	(A)	Drug content (mg)	Volume (ml)
<b>1A</b>	1250mg	412.4	0.630	192.6	13.9	137.3	0.198	77.5	22.6
<b>1B</b>	1131mg	405.6	0.641	189.9	13.7	139.4	0.195	77.2	22.5
<b>1C</b>	1125mg	415.2	0.627	195.4	14.1	138	0.197	77.2	22.5
<b>1D</b>	1115mg	413.2	0.629	194	14.0	143.8	0.189	78.4	22.9
<b>1E</b>	1130mg	404.8	0.642	195.4	14.1	152.7	0.178	79.7	23.2

A = refers to absorbance value

Table 4.2.3 shows values of the percentage content of the four in the assayed 4FDC drug samples. One sample out of five was not compliant with the BP 2008 specification for content of active ingredient as a percentage. Sample 1E had 106.3% of Isoniazid and fell above the BP specification of 95 – 105%.

**Table 4.2.3 Percentage content of four drugs in 4FDC samples**

<b>Drug Code</b>	<b>Pyrazinamide</b>	<b>Ethambutol</b>	<b>Rifampicin</b>	<b>Isoniazid</b>	<b>Result</b>
<b>1A</b>	103.1%	96.3%	94.4%	103.3%	Pass
<b>1B</b>	101.4%	95.0%	95.9%	102.9%	pass
<b>1C</b>	103.8%	97.7%	94.9%	102.9%	Pass
<b>1D</b>	103.3%	97.6%	98.9%	104.6%	Pass
<b>1E</b>	101.2%	97.7%	105.0%	<b>106.3%</b>	<b>Fail</b>

### 4.3 3FDC

Table 4.3.1 shows identification results of the three drugs that were contained in 3FDC samples that were tested. All the three drugs gave a positive test result for identification for all the five samples that were tested.

**Table 4.3.1 Drug identification test results for the drugs in 3FDC samples**

<b>Drug Code</b>	<b>Ethambutol</b>	<b>Rifampicin</b>	<b>Isoniazid</b>	<b>Result</b>
<b>2A</b>	+	+	+	Pass
<b>2B</b>	+	+	+	Pass
<b>2C</b>	+	+	+	Pass
<b>2D</b>	+	+	+	Pass
<b>2E</b>	+	+	+	Pass

*+= Positive identification test*

Table 4.3.2 shows the mean tablet weights for the sampled 3FDC. It also shows the calculated drug content for each drug that constitute 3FDC drugs as well as the absorbance values and the volumes of titrated perchloric acid for Ethambutol and Potassium bromide for Isoniazid used to calculate the drug content and consequently the percentage content of each individual drug in the fixed dose combination drug samples.

**Table 4.3.2 Drug content values for the three drugs in 3FDC samples**

Drug Code	Mean tablet weight (mg)	Ethambutol		Rifampicin		Isoniazid	
		Drug content (mg)	Volume (ml)	Drug content (mg)	(A)	Drug content (mg)	Volume (ml)
<b>2A</b>	745	191.3	13.8	143.8	0.189	78.4	22.9
<b>2B</b>	760	189.9	13.7	146.9	0.185	77.8	22.7
<b>2C</b>	740	195.4	14.1	146.1	0.186	78.2	22.8
<b>2D</b>	750	191.3	13.8	155.3	0.175	78.2	22.8
<b>2E</b>	750	192.6	13.9	146.1	0.186	77.5	22.6

A= refers to absorbance values

Table 4.3.3 shows values of percentage content of the three drugs contained in 3FDC samples that were tested and all the five samples were found to be compliant to the specifications of the BP 2008 which was the official monograph that was used.

**Table 4.3.3 Values of percentage content of the three drugs in 3FDC samples**

<b>Drug Code</b>	<b>Ethambutol</b>	<b>Rifampicin</b>	<b>Isoniazid</b>	<b>Result</b>
<b>2A</b>	95.6%	98.9%	104.6%	Pass
<b>2B</b>	95.0%	101.0%	103.7%	Pass
<b>2C</b>	97.7%	100.5%	104.2%	Pass
<b>2D</b>	95.6%	106.8%	104.2%	Pass
<b>2E</b>	96.3%	100.5%	103.3%	Pass

#### **4.4 2FDC (Rifinah)**

Table 4.4.1 shows identification test results of the drugs that were contained in the 2FDC drug samples. The results showed a 100% positive identification test result for all the samples that were tested.

**Table 4.4.1 Identification test results for individual drugs in Rifinah drug samples**

<b>Drug Code</b>	<b>Rifampicin</b>	<b>Isoniazid</b>	<b>Result</b>
<b>3A</b>	+	+	Passed
<b>2B</b>	+	+	Passed
<b>3C</b>	+	+	Passed
<b>3D</b>	+	+	Passed
<b>3E</b>	+	+	Passed
<b>3F</b>	+	+	Passed
<b>3G</b>	+	+	Passed

+ = *Positive identification test*

Table 4.4.2 shows the calculated drug content figures Rifampicin and Isoniazid in the Rifampicin samples. The table also shows the absorbance values for Rifampicin that were used to calculate the drug content figures as well as the volumes of Potassium Bromide used to calculate the drug content values of Isoniazid.

**Table 4.4.2 Drug content values for Rifampicin and Isoniazid in Rifinah samples.**

Drug Code	Mean Weight per Tablet (mg)	Rifampicin		Isoniazid	
		Drug content per tablet (mg)	(Absorbance)	Drug content Per tablet (mg)	Volume of perchloric acid Used (ml)
<b>3A</b>	375	138	0.197	77.5	22.6
<b>3B</b>	375	139.4	0.195	77.5	22.6
<b>3C</b>	380	139.4	0.195	78.5	22.9
<b>3D</b>	360	142.3	0.191	79.2	23.1
<b>3E</b>	380	140.1	0.194	78.2	22.8
<b>3F</b>	375	142.3	0.191	77.8	22.7
<b>3G</b>	370	144.6	0.188	78.2	22.8

Table 4.4.3 shows values of percentage content of the two drugs in 2FDC samples that were tested and one out of seven samples was not compliant the BP 2008 specifications. Sample 3D had 105.6% of Isoniazid and fell above the accepted range of 95% - 105%.

**Table 4.4.3 Values of percentage content of the two drugs in Rifinah samples**

<b>Drug Code</b>	<b>Rifampicin</b>	<b>Isoniazid</b>	<b>Result</b>
<b>3A</b>	94.9%	103.3%	Passed
<b>2B</b>	95.9%	103.3%	Passed
<b>3C</b>	95.9%	104.6%	Passed
<b>3D</b>	97.9%	<b>105.6%</b>	<b>Fail</b>
<b>3E</b>	96.4%	104.2%	Passed
<b>3F</b>	97.9%	103.8%	Passed
<b>3G</b>	99.4%	104.2%	Passed



## **CHAPTER 5**

### **5.0 DISCUSSION**

This cross sectional study that was conducted in Lusaka District to assess the quality of fixed dose combination anti Tuberculosis drugs from the clinics which were the points of distribution to the patients provides vital information on the quality of drugs that are being used for the treatment of Tuberculosis in the national TB programme. The results of the study provide objective information on the quality of drugs in terms of presence of active ingredient as well as the actual percentage content of each active ingredient for each sample that was tested.

Quality can be defined as a combination of attributes a product which determine its degree of acceptability as the right product for the intended use and is capable of exerting the correct pharmacological action when used correctly. The quality of a pharmaceutical product will therefore depend on the degree of adherence to the general manufacturing practices and the packaging materials used to package the product as well as the storage conditions that the pharmaceutical product is subjected to after manufacture. When any one of the above is not addressed adequately the result is a pharmaceutical product that is none compliant with the official monographs that provide guidance on the specifications for quality.

The identification tests for individual drugs that were contained in the fixed dose combination formulations yielded positive results for all the samples that were tested. This means that all the samples that were tested yielded a 100% positive identification test for the individual components of the fixed dose combination formulations line with the label claims of each category of the fixed dose combination formulation. All the 4FDC samples contained the four drugs indicated on the label and these included Pyrazinamide, Ethambutol, Rifampicin and

Isoniazid. All the 3FDC samples contained the three drugs indicated on the label for 3FDC and these drugs comprised Ethambutol, Rifampicin and Isoniazid and the 2FDC samples also contained the two drugs as indicated on the label which included Rifampicin and Isoniazid.

All the samples that were collected for analysis from health facilities had a similar type of packaging. They were all packaged in blister packs that were unbroken and each blister pack contained twenty eight tablets. The blister packs were intact and moisture entry into the packaging was not likely to happen. These blister packs were then packed in card board boxes. The card board boxes provided protection of the tablets from direct sunlight that could otherwise affect the quality of the tablets by accelerating the of the individual drugs in the fixed dose combination formulations. However, the labeling on the blister packs was not very clear and legible. It was clear though on the card board boxes where the blister packs were packed.

The findings of the study on the percentage content of active ingredients confirmed the existence of substandard drugs availed to the general public and this is of great concern especially in the treatment of infectious diseases such as Tuberculosis. This is especially so because in the study 1/5 of the 4FDC samples were found to be none compliant to the BP 2008 specification for percentage content. Isoniazid was found to fall above the BP specification of 95 – 105% with a percentage content of 106.4%.

All the 3FDC samples were found to be compliant to the BP 2008 specifications for percentage content. In the 2FDC samples comprising Rifampicin and Isoniazid 1/7 of the samples were found to be none compliant to the BP 2008 specification for percentage content of 95 – 105%. Isoniazid was found to have a percentage content of 105.6% which was above the BP 2008

specification. It is important to note that Isoniazid is the drug that was found to be compromised in one sample of 4FDC and 2FDC.

The findings that 1/5 of 4FDC and 1/7 of 2FDC did not comply with the BP 2008 specifications for percentage content entails that there is urgent need to strengthen and scale up monitoring activities aimed at improving quality control of all Pharmaceutical products before they are released to the general public for consumption. It is important to put deliberate procedures and policies in place to ensure that drugs that are manufactured locally are assessed for quality by an independent body such as the Pharmaceutical Regulatory Authority other than the manufacturers in order to prevent offloading of substandard drugs to the general public. Similarly for those drugs that are imported into the country it is essential to verify the information that is provided by the manufacturers by subjecting these pharmaceutical products to quality control. The basic aim of these monitoring activities is to ensure that all drugs meet the required specifications for quality as stipulated in the official monographs.

## **5.1 CONCLUSION**

This study has shown that substandard anti Tuberculosis drugs are present in Lusaka district. The results have shown that 1 in 5 of the samples for 4FDC were none compliant for Isoniazid to the BP 2008 specifications for percentage content and 1 in 7 of the samples for 2FDC were none compliant to the BP 2008 specifications for percentage content for Isoniazid.

These results confirm the urgent need to strengthen the capacity of the Pharmaceutical Regulatory Authority (PRA) so that it is able to carry out monitoring activities on drugs that come into the country and those that are manufactured locally before these drugs are released to the general public. This will ensure safety and efficacy of the drugs that are used in the country and will in turn improve on treatment outcome for the majority of the Zambians who depend on these drugs for their survival from curable diseases.

## **5.2 RECOMMENDATIONS**

The findings of this study that was carried out in Lusaka district on fixed dose combination anti TB drugs have established that substandard drugs are present in Lusaka district. This has serious implications on treatment outcome and patient survival. In view of this the following recommendations are made;

- The Ministry of Health should establish a National Quality Control Laboratory that should be supported by satellite mini labs at the points of entry for drugs.
- The PRA should strengthen post marketing surveillance of drugs that should cover the country.

### 5.3 STUDY LIMITATIONS

- At the time of this study the private hospitals that were included in the study were getting their anti TB drug supplies from the Ministry of Health through a partnership that was to help provide free anti TB services to patients in these private hospitals. This means that a comparison of the quality of the drugs between government and private hospitals / clinics was not possible since the drugs were from the same source. If this was not the case private institutions would probably have preferred to use cheaper sources hence substandard drugs.
- High Performance Liquid Chromatography (HPLC) was not used to assign possible reasons for the poor quality drugs detected due to financial constraints.

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## APPENDICES

### APPENDIX I. BUDGET

Description	Responsible person	Daily	Numbers personnel	Working days /week	Duration of acting	Total cost(ZK)
Personnel emoluments	Research assistants	50,000=00	2	4	2weeks	800 000.00
	Laboratory quality control Manager	250 000.00	1	4	2 weeks	2 000 000.00
	Research statistician	250,000.00	1	4	2 weeks	2 000 000.00
					Subtotal	K6,800 000.00
Supplies	Item	Unit Pack	Quantity Required	Unit Cost		Total Cost
	Paper	Ream	3	50,000.00		150,000.00
	Ball point pens	Each	4	2000.00		8 000.00
	Pencils	Each	4	2000.00		8 000.00
	Stapler	Each	1	100 000.00		100 000.00
	Staples	Each	1	35 000.00		35 000.00
	Punch	100	1	150 000.00		150 000.00
	Hiring of laboratory facility			2,000 000.00		2,000 000.00
	Reagents	Each	1	2,500 000.00		2,500 000.00
						K4,951 000.00

Purchase of samples	4FDC	56	5			000 000.00
	3FDC	56	5			000 000.00
	2FDC	56	7			000 000.00
					Subtotal	
Travel expenses	From UTH to research areas & back					K2,500 000.00
					Grand Total	ZK 14,251,000.00

**APPENDIX II: DRUG COLLECTION SHEET**

**UNIVERSITY OF ZAMBIA**

SCHOOL OF MEDICINE

**DEPARTMENT OF COMMUNITY MEDICINE**

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FIXED DOSE COMBINATION ANTI TUBERCULOSIS DRUG COLLECTION FORM

Name of drug: \_\_\_\_\_

Batch number \_\_\_\_\_

Components: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Date of manufacture: \_\_\_\_\_

Expiry date: \_\_\_\_\_

Manufacturer: \_\_\_\_\_

Condition of tablets: \_\_\_\_\_

Number of tablets collected: \_\_\_\_\_

Type of packaging material: \_\_\_\_\_

Cost of sample: \_\_\_\_\_

Source of sample: \_\_\_\_\_ [Code only] (private hospital)

Date of sample collection: \_\_\_\_ / \_\_\_\_ / \_\_\_\_

Signature of researcher: \_\_\_\_\_ Date: \_\_\_\_ / \_\_\_\_ / \_\_\_\_\_

Signature of Pharmacist / Dispenser: \_\_\_\_\_ Date: \_\_\_\_ / \_\_\_\_ / \_\_\_\_\_

### APPENDIX III: VARIABLES AND INDICATORS

VARIABLES	INDICATORS	SCALE OF MEASUREMENT
content of active ingredient	Percentage Content	92.5% to 107.5% (Rifampicin)  95% to 105% (Pyrazinamide,  Ethambutol, and  Isoniazid)
Active ingredient	content	<ol style="list-style-type: none"> <li>1. 4FDC (pyrazinamide, Rifampicin, Ethambutol and Isoniazid)</li> <li>2. 3FDC (Ethambutol, Rifampicin, and Isoniazid)</li> <li>3. 2FDC (Rifampicin and isoniazid)</li> </ol>
Labeling	Information on the label	
Packaging	Packaging material	

## APPENDIX IV: LETTER OF PERMISSION TO USE THE LABORATORY

The University of Zambia  
School of Medicine  
P. O. Box 50110,  
Lusaka.

2<sup>nd</sup> February 2010

The Managing Director  
Tejay Pharmaceutical Limited  
Lusaka  
U.F.S. The Head of Department  
Department of Community Medicine  
The University of Zambia  
Lusaka

Dear Sir/Madam,

RE: REQUEST FOR PERMISSION TO CARRY OUT A RESEARCH ENTITLED “AN  
EVALUATION OF THE QUALITY OF FIXED DOSE COMBINATION (FDC) ANTI  
TUBERCULOSIS DRUGS IN LUSAKA DISTRICT

I am a University of Zambia student pursuing a Masters Degree programme in Public Health and I am doing a research entitled an evaluation of the quality of fixed dose combination (FDC) anti TB drugs in Lusaka Province.

I am requesting your esteemed office to allow me use your laboratory facilities to analyze the samples of the FDC anti TB drugs in order to verify the quality of the drug samples for the study.

I will be grateful if my requests will be favorably considered.

Yours sincerely,

Warren Mweemba

APPENDIX V: LETTER OF PERMISSION TO COLLECT SAMPLES FROM PUBLIC INSTITUTIONS.

The University of Zambia  
School of Medicine  
P. O. Box 50110  
Lusaka  
2<sup>nd</sup> February 2010

The Permanent Secretary  
Ministry of Health  
Ndeke House  
Lusaka  
U.F.S. The Head of Department  
The University of Zambia  
Community Medicine  
Lusaka

Dear Sir/Madam,

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

I am a University of Zambia student pursuing a Masters Degree programme in Public Health. As a requirement for the award of the Masters Degree certificate, I am undertaking a research entitled “evaluation of the quality of fixed dose combination (FDC) anti tuberculosis tablets available in Lusaka district”.

I am requesting for permission to collect fixed dose com (FDC) anti TB drug samples from government institutions where these drugs are dispensed from.

I will be grateful if my request will be granted.

Yours sincerely,

Warren Mweemba



## APPENDIX VI: GHANT CHART

Description of activity	January 2010	February 2010	March 2010	April 2010	May 2010	June 2010	July 2010	August 2010	September 2010	October 2010	November 2010	December 2010
Presentation at the UNZA graduation forum												
Presentation to the Research ethics committee												
Training of research assistant												
Sample collection												
Sample analysis												
Report writing												
Submission of Research report												