QUALITY ASSESSMENT OF FOUR FIXED DOSE COMBINATION ANTI-
TUBERCULOSIS DRUGS IN GOVERNMENT FACILITIES IN MOMBASA,
KILIFI, KWALE AND NAIROBI COUNTIES

BIBIANA K. NJUE (B.PHARM)

Registration No. 1 57/11274/04

A RESEARCH THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE
REQUIREMENT FOR THE DEGREE OF MASTER OF PUBLIC HEALTH IN THE
SCHOOL OF PUBLIC HEALTH OF KENYATTA UNIVERSITY

October 2013
DECLARATION

“This thesis is my original work and has not been presented for a degree or other awards in any other university”

Signature------------------------------------- Date-------------------------

Name: Bibiana K. Njue
Department of Community Health

SUPERVISORS:

We confirm that the work reported in this thesis was carried out by the candidate under our supervision.

Prof. Nicholas K. Gikonyo
Department of Pharmacy and Complementary /Alternative Medicine
Kenyatta University

Signature------------------------------- Date----------------------

Prof. Gilbert Kokwaro
School of Pharmacy
University of Nairobi

Signature-------------------------------------- Date----------------------
DEDICATION

To my husband Eng. Elton Njue, and children, Arnold Muchiri, Caroline Wawira, Linet Muthoni and Timothy Mwaniki for giving me a reason to go on in life.
ACKNOWLEDGEMENTS

My profound and sincere gratitude go to my supervisors, Prof. Nicholas Gikonyo and Prof. Gilbert Kokwaro, for the assistance, support and guidance given to me in this work from inception to its completion. I would like to thank Pharmacy and Poisons Board (PPB) management for sponsoring collection of samples in Nairobi and Coast counties as well as the analysis of these samples in the National Quality Control Laboratory (NQCL). I also appreciate Dr. Jayesh Pandit of PPB and Dr. Chris Masila of National Leprosy and Tuberculosis Programme (NLTP) for assisting me in sample collection. I will not forget to thank the analyst Mr. Nehemiah Birgen of NQCL who worked with me in analyzing the four fixed dose combination (FDC) anti-tuberculosis samples. Appreciation also goes to all the authorities in Nairobi and Coast, for approval given to collect samples from the health centers, all health workers who assisted in data collection. Mr. Bernard Muture of National Public Health Laboratory Services assisted in the data analysis for this thesis; to him I say a big thank you. May the almighty God continuously show you his favour. Finally, I thank the almighty God for life, for his all sufficient grace, and without whom this work would not have been completed.
# TABLE OF CONTENTS

DECLARATION ............................................................................................................. ii
DEDICATION .................................................................................................................. iii
ACKNOWLEDGEMENTS ................................................................................................. iv
TABLE OF CONTENTS ................................................................................................. v
LIST OF TABLES ............................................................................................................. x
LIST OF TABLES ............................................................................................................. x
LIST OF FIGURES ......................................................................................................... xi
ABBREVIATIONS AND ACRONYMS ............................................................................ xii
DEFINITION OF TERMS ................................................................................................. xiv
ABSTRACT ...................................................................................................................... xv

## CHAPTER ONE: INTRODUCTION............................................................................... 1

1.1 Background of the study ......................................................................................... 1
1.3 Study Justification .................................................................................................. 6
1.4 Research Questions ................................................................................................ 6
1.5 Hypothesis .............................................................................................................. 7
1.6 General Objective .................................................................................................. 7
1.7 Specific Objectives ................................................................................................. 7
1.8 Significance and anticipated outcome .................................................................... 7
1.9 Delimitation and Limitation of the study ............................................................... 8
  1.9.1 Delimitation ..................................................................................................... 8
  1.9.2 Limitation ..................................................................................................... 8
1.10 Conceptual Framework ......................................................................................... 8
CHAPTER TWO: LITERATURE REVIEW

2.1 Tuberculosis

2.1.1 Aetiology of Tuberculosis

2.1.2 Tuberculosis Epidemiology and Spread of Tuberculosis

2.1.3 The burden of Tuberculosis

2.1.4 Tuberculosis and HIV/AIDS

2.1.6 Control of Tuberculosis

2.1.7.1 Treatment of Tuberculosis using Fixed Dose Combination

2.1.8 Drug resistance to Mycobacterium tuberculosis

2.2 Quality Assessment of anti-TB drugs

2.2.1 Formulation

2.2.2 Packaging of anti-TB drugs

2.2.3 Storage of anti-TB drugs

2.2.4 Monitoring Humidity

2.3 Global quality concerns of anti-TB drugs

2.4 Tuberculosis treatment targets

2.5 WHO definition of a substandard drug

2.6 Drug quality concerns in developing countries

CHAPTER THREE: METHODOLOGY AND RESEARCH DESIGN

3.1 Study Areas

3.2 Study Population

3.3 Study Design

3.4.1 Dependent variable
3.4.2 Independent Variables ................................................................. 30
3.5 Target Units of Study ................................................................... 30
3.6 Inclusion Criteria ......................................................................... 30
3.7 Exclusion Criteria ......................................................................... 30
3.8 Sampling Techniques .................................................................... 31
3.9 Sample Size Determination ............................................................ 31
3.10 Research Instruments .................................................................. 32
3.11 Validity ......................................................................................... 33
3.12 Data Collection Method ................................................................. 33
  3.12.1 Uniformity of weight ................................................................. 33
  3.12.2 Friability .................................................................................. 34
  3.12.4 Assay for determination of active Ingredients ................................ 35
  3.12.5 Analytical procedures ............................................................... 38
    3.12.5.1 Chemical reference standards .......................................... 39
    3.12.5.2 Instrumentation ................................................................. 39
    3.12.5.3 Chromatographic conditions .......................................... 39
    3.12.5.4 Sample Preparation .......................................................... 40
3.13 Data Management and Analysis ..................................................... 40
3.14 Ethical Consideration .................................................................... 40

CHAPTER FOUR: RESULTS ................................................................... 41
  4.1 Characteristics of sample population ............................................. 41
  4.2 Compliance of anti-TB FDC drugs with International Pharmacopoeia specifications ............................................................. 42
4.2.1 Uniformity of Weight of FDC drugs ................................................................. 42
4.2.2 Friability ................................................................................................................. 43
4.2.3 Dissolution of anti-TB FDC drugs by facility ....................................................... 44
4.2.4 Assay of active ingredients in FDC Tablets ......................................................... 46
4.2.5 Overall Analysis of compliance of FDC tablets .................................................... 48
4.3 Association of Quality of FDC drugs between Health facilities and KEMSA ........... 50
4.5 Storage conditions practiced by health facilities for the Fixed Dose Combination anti-tuberculosis drugs ......................................................................................... 54

CHAPTER 5: DISCUSSION ......................................................................................... 56

5.2. Dissolution of FDC Tablets ................................................................................. 58
5.3 Friability .................................................................................................................... 58
5.5 Compliance to specifications of drug samples in KEMSA and Health Centers . 59

CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS .................................. 62

6.1 Conclusions ............................................................................................................ 62
6.2 Recommendations ................................................................................................. 64

iii. The Pharmacy and Poisons Board should continuously monitor the quality of anti-TB drugs in the market .................................................................................. 64

6.3 Suggestions for further study .................................................................................. 64

REFERENCES .............................................................................................................. 65

APPENDICES ............................................................................................................. 68

APPENDIX 1a: Study area (Nairobi County) ................................................................. 68
APPENDIX 1b: Study area (Coast Counties)................................................................. 69
APPENDIX 2: DATA COLLECTION TOOLS ................................................................. 70
APPENDIX 3: AUTHORITY TO CONDUCT RESEARCH ....................................... 73
APPENDIX 4: CERTIFICATES OF ANALYSIS ............................................. 74
APPENDIX 5: CHROMATOGRAMS ............................................................ 80
LIST OF TABLES

Table 3.1: Sampled facilities and Number of tablets................................................................. 28
Table 3.2: Number of sampled tablets by manufacturer............................................................ 28
Table 3.3: Mobile phase.................................................................................................................. 36
Table 4.1: Uniformity of weight for Fixed Dose Combination by Facility................................. 42
Table 4.2: Friability of anti-TB Fixed Dose Combination by Facility ........................................... 43
Table 4.3: Dissolution of Ethambutol............................................................................................ 45
Table 4.5: Dissolution of Isoniazid in the Fixed Dose Combination by Facility....................... 45
Table 4.4: Dissolution of Rifampicin in the Fixed Dose Combination by facility ...................... 45
Table 4.6: Dissolution of Pyrazinamide in the Fixed Dose Combination by Facility ............... 46
Table 4.7: Assay of Ethambutol in the Fixed Dose Combination per Facility............................ 47
Table 4.8: Assay of Rifampicin in Fixed Dose Combination per Facility..................................... 47
Table 4.9: Assay of Isoniazid in the Fixed Dose Combination per Facility............................... 48
Table 4.10: Assay of Pyrazinamide in the Fixed Dose Combination per Facility....................... 48
Table 4.11: Overall compliance with specifications (weight, friability, dissolution and assay).......................................................................................................................... 50
Table 4.12: Association of Quality of Fixed Dose Combination drugs between Health facilities and KEMSA.................................................................................................................. 52
Table 4.13: Association of Quality of Fixed Dose Combination drugs between Coast and Nairobi Facilities.................................................................................................................. 53
Table 4.14: Storage conditions practiced for the Fixed Dose Combination anti-tuberculosis drugs ........................................................................................................................................ 55
LIST OF FIGURES

Figure 1.1: Conceptual framework of the study ................................................................. 10

Figure 4.1 Compliance of Fixed Dose Combination anti-TB drugs in the sampled facilities................................................................. 49
ABBREVIATIONS AND ACRONYMS

AFB  Acid Fast Bacilli
AIDS  Acquired Immunodeficiency Syndrome
API  Active Pharmaceutical Ingredient
CDR  Case Detection Rate
DARU  Drug Analysis Research Unit
DG  Director General
DOTS  Directly Observed Treatment Short Course
DTLCs  District TB Leprosy Coordinators
DLTLD  Division of Leprosy, Tuberculosis and Lung disease
DQI  Drug Quality and Information
E  Ethambutol
EDL  Essential Drug List
FDC  Fixed Dose Combination
FEFO  First Expiry First Out
FHI  Family Health International
FIFO  First in First Out
FPP  Finished Pharmaceutical Product
GDF  Global Drug Facility
GMP  Good Manufacturing Practices
GOK  Government of Kenya
H  Isoniazid
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HPLC</td>
<td>High Pressure Liquid Chromatography</td>
</tr>
<tr>
<td>HYD</td>
<td>Hydrazone</td>
</tr>
<tr>
<td>IUATLD</td>
<td>International Union against Tuberculosis and Lung Disease</td>
</tr>
<tr>
<td>KEBS</td>
<td>Kenya Bureau of Standards</td>
</tr>
<tr>
<td>KEMSA</td>
<td>Kenya Medical Supplies Agency</td>
</tr>
<tr>
<td>MOH</td>
<td>Ministry of Health</td>
</tr>
<tr>
<td>MSH</td>
<td>Management Sciences for Health</td>
</tr>
<tr>
<td>NLTP</td>
<td>National Leprosy and Tuberculosis Program</td>
</tr>
<tr>
<td>NTM</td>
<td>Non-tuberculous mycobacteria</td>
</tr>
<tr>
<td>NQCL</td>
<td>National Quality Control Laboratory</td>
</tr>
<tr>
<td>PPB</td>
<td>Pharmacy and Poisons Board</td>
</tr>
<tr>
<td>QA</td>
<td>Quality Assurance</td>
</tr>
<tr>
<td>R</td>
<td>Rifampicin</td>
</tr>
<tr>
<td>RSD</td>
<td>Relative Standard Deviation</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for Social Sciences</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>UNCHR</td>
<td>United Nation High Commission for Refugees</td>
</tr>
<tr>
<td>USP</td>
<td>United States Pharmacopoeia</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>Z</td>
<td>Pyrazinamide</td>
</tr>
</tbody>
</table>
DEFINITION OF TERMS

**Quality:** Involves all the characteristics of Purity, strength, packaging and labelling that allow the drug to deliver its intended treatment.

**Storage:** Is the storing of pharmaceutical product up to their point of use

**Substandard drug:** A legal branded or generic drug that does not meet National or International standards for quality, purity, strength or packaging.

**Counterfeit drug**
A counterfeit drug is one which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging.

**United States Pharmacopeia and National Formulary (USP-NF)** is an authoritative source of recommended specifications and other information for therapeutic products including drug substances and recipients. It receives legal recognition under US Food, Drug and Cosmetics act. It provides a uniform and public basis on which to evaluate therapeutic products used in the practice of medicine and pharmacy.
ABSTRACT

The four fixed dose combination (FDC) anti-Tuberculosis (TB) drugs that the Kenyan government supplies through the National Leprosy and Tuberculosis Programme (NLTP) to the health facilities must be of high quality and effective in order to ensure success in TB treatment. According to Global Drug Facility (GDF), treatment of TB with poor quality anti-TB drugs could result in treatment failures as well as leading to drug resistance to *Mycobacterium tuberculosis*. It also has deleterious effects on the health of the wider population in Kenya. The NLTP is yet to achieve the internationally set targets of 85% cure rates of all detected TB cases. Although drugs have been registered by the Pharmacy and Poisons Board (PPB), under the Ministry of Health, their quality has not been regularly assured. The World Health Organization (WHO) estimates that up to 25% of drugs used in developed and developing countries are substandard. Therefore the main objective of the study was to assess the quality of anti-TB drugs supplied by NLTP to different levels of healthcare alongside internationally set standards in Mombasa, Kwale, Kilifi and Nairobi Counties and assess the storage conditions in the health facilities and in Kenya Medical Supplies Agency (KEMSA). The drugs were randomly sampled from eight health facilities in Nairobi, Mombasa, Kilifi and Kwale counties. Data on storage conditions was collected through a questionnaire administered at the time of collection of samples as well as through observation method. The drugs were analyzed for content, dissolution, uniformity of weight and friability in the National Quality Control Laboratory (NQCL). Results from the laboratory were entered in the computer and using the SPSS software version 11.5 was analyzed by descriptive statistics. The results indicated that uniformity of weight of all drugs sampled in all facilities complied with the specifications. Friability specifications for the drugs from seven facilities out of eight (87.5 %) complied. It is only the drugs from Diani health center that did not meet the specifications. Dissolution specification for Rifampicin was not met in 3 of 8 (37.5%) facilities. The specifications for dissolution of Isoniazid, Ethambutol, and Pyrazinamide were met in all the facilities. The assay of drugs for Rifampicin from 5 of the eight facilities (62.5%) was less than 90% thus failed to comply with the specification. Assay for Ethambutol was 112% which was outside the limits thus failed the test. Assay for the Isoniazid and Pyrazinamide from all the eight facilities complied. All samples from KEMSA and the Health Centers complied with specifications with regard to uniformity of weight and dissolution of Ethambutol, Isoniazid and Pyrazinamide as well as with respect to assays for Isoniazid and Pyrazinamide. For these tests, there was no difference on quality between drugs sampled from KEMSA and the Health Centers. Results from tests on friability and assays of Ethambutol indicated that one health facility out of eight (12.5%) failed to comply while samples from all KEMSA sites complied. There was better compliance of drugs from the Health Centers on dissolution and assay of Rifampicin than from KEMSA. Overall, drugs from all health facilities failed to comply with the specifications for various reasons. This study suggested that regular post market surveillance in all health facilities should be carried out as well as a regular storage facilities assessment.
CHAPTER ONE: INTRODUCTION

1.1 Background of the study

Tuberculosis (TB) is an infectious disease caused by a bacterium called *Mycobacterium tuberculosis*. *Mycobacterium* is a genus of gram-positive, rod shaped bacteria, which is free living and pathogenic. Occasionally *Mycobacterium bovis*, transmitted through contaminated milk and *Mycobacterium africanum* may also cause the disease. The bacteria are transmitted from person to person through aerosolized droplet nuclei. Coughing, which generates infected droplets, is the most important mode of transmission of TB. The bacteria may also be transmitted by other aerosol generating processes including laughing, talking, sneezing, singing and spitting. The infectious patient is that person with a sputum smear positive ((NLTP, 2006). Sputum smear positive in pulmonary TB case is based on the presence of at least one acid fast bacilli (AFB) in one sputum sample microscopically.

Tuberculosis is a public health problem in Kenya. Kenya is ranked 10th among the 22 TB high burden countries. It is estimated that there are 338 cases of TB per 100,000 populations (DLTLD, 2009) and HIV /AIDS is reported to be the main driver of all TB patients. It has been found that 45% of all TB patients are found to be HIV positive. Multi Drug Resistant TB (MDR-TB) in Kenya is low but indicators are that it is growing. Kenya adopted the Directly Observed Treatment Short Course (DOTS) over twenty years ago and the WHO TB control set targets of 70/85 has not been achieved. That is Case Detection Rate (CDR) of 70% and the treatment cure rate of all cases detected at 85%. The treatment success rate has been at 80% since the adoption of DOTS and the case detection rate was 47% in 2004 (NLTP, 2006).
The Commonly used drugs in treatment of tuberculosis are Isoniazid (H), Rifampicin(R), Ethambutol (E), and Pyrazinamide (Z) in a fixed combination of the four drugs. These drugs must be of high quality, uninterrupted supply and in adequate quantities to ensure continuity of therapy. One of the objectives of the National Drug Policy is, to ensure that the quality of drugs that are locally manufactured and that are imported meet internationally accepted quality standards (MOH, 1994).

A study conducted by the Drug Analysis Research Unit (DARU) in the University of Nairobi Kenya, indicated that the failure rate of all drugs analyzed including monotherapy anti-TB drugs, during the years 1996-2000 was 24.6% (Thoithi et al., 2002). This however, did not include the four fixed dose combination anti-TB drugs, used in tuberculosis treatment. Climatic conditions especially excessive heat, light and moisture, which have been known to affect the stability of the four fixed dose combination anti-tuberculosis drug were not investigated either. Previous studies had shown that Ethambutol in the combination though blister packed had showed a high rate of moisture absorption in the presence of light (Kenyon et al., 1999).

In a study done in India by Bhutani et al. (2004) in which the physical and chemical stability of anti-tuberculosis fixed-dose combination products under accelerated climatic conditions indicated that Rifampicin degraded by 13-20% after storage for 12 days under 40°C degrees and 75% Relative humidity. The study also indicated that blister packed FDCs containing Ethambutol, showed a higher rate of moisture uptake in the presence of light.

In a similar study done by Kenyon et al. (1999) in Gaborone, Botswana whereby the objective was to determine the actual versus stated content of drugs in the FDCs indicated
that 31% of the FDCs that were analyzed had substandard content, especially the low content of Rifampicin, the most important bactericidal TB drug in the FDCs, was of great concern. It was explained that the cause of poor drug quality could be poor manufacturing practices, counterfeiting or inappropriate drug storage in excessive heat, moisture or light.

There is no report on the assessment of quality of the four fixed dose anti-TB drugs on the Kenyan market and in the public health facilities implying that quality of these drugs in market is unknown. It is important to establish the quality of anti-TB drugs the National Leprosy and Tuberculosis Programme (NLTP) distributes to health facilities from Kenya Medical Supplies Agency (KEMSA). According to the Daily Observed Treatment strategy (DOTS), only drugs that are safe, effective and of high quality should be issued to patients suffering from tuberculosis. The government of Kenya has entrusted KEMSA with the responsibility of procuring drugs of high quality through competitive bidding. However there is no follow up, after purchase and distribution of anti-TB drugs to ensure that the quality of the drugs at the final distribution points is maintained. The main traditional measure of drug quality is an assay value of the active ingredient of a drug expressed as percentage of the stated label content. This has to comply with the pharmacopoeia specifications being used (USP, 2006).

Several studies conducted indicate that substandard anti-TB drugs are available in the global market (Laserson et al. 2001). According to the United States Pharmacopoeia (USP) Drug Quality and Information (DQI) Training Manual on Good Laboratory Practices, Basic Tests, and Sampling Procedures, the final drug quality of a manufactured product is determined by raw starting ingredient(s), formulation, manufacturing process
and equipment, technical know-how for producing and packaging it, transportation and storage conditions (USP, DQI 2003). Fixed dose combinations (FDCs) of anti-tuberculosis drugs (Rifampicin, Isoniazid, Pyrazinamide and Ethambutol hydrochloride) have several advantages over loose combinations of these drugs. Hence, the use of FDCs in the short course chemotherapy of tuberculosis is being promoted internationally. However, these products are associated with quality problems such as loss of bio-availability of Rifampicin and instability of the drugs in the combination. (Saranjit et al., 2006).

The objective of this study therefore was to assess the quality of four fixed dose combination anti-TB drugs supplied by NLTP to different levels of public health care facilities with a view to providing information on quality of FDCs anti-TB drugs available in health facilities and that are used in the intensive phase of TB treatment. A substantial number of anti-TB drugs from several countries, particularly fixed-dose combinations, were found to be substandard.

1.2 Problem Statement

WHO estimates that up to 25% of the medicines used in developing and developed countries are counterfeit or substandard. In developing countries, medicines used to treat life threatening conditions such as malaria, TB and Human Immunodeficiency Syndrome (HIV/AIDS) are commonly found to be counterfeit (ICN, 2005).

Various studies done in Africa and India on four fixed dose combination anti-TB drugs have showed that the drug is physically and chemically unstable under accelerated conditions (40°C degrees and 75 Relative Humidity). Ethambutol in the combination was
shown to draw moisture due to its hygroscopic nature into the drug, thereby creating a liquid environment good for degradation of the drug in combination (Kenyon et al., 1999).

Despite regular provision of anti-TB drugs by the Government of Kenya (GOK) through the NLTP, the set target by WHO to treat 85% successfully of all TB detected cases has not been achieved (NLTP, 2005). Information on the quality of fixed dose anti-TB drugs in Kenya is lacking and therefore the need for FDCs assessment of quality in government facilities and also assess the storage conditions practiced by the staff in these facilities. No study has been done to assure that the anti-TB drugs are safe, effective and of high quality especially the four fixed dose combination that has been shown to lead to poor bioavailability of Rifampicin (Bhutani et al., 2004).

The anti-TB drugs are distributed and stored in district stores, from where the health centers and dispensaries are supplied from. Infrastructures in most public health facilities are sub-optimal and especially in hot and humid climatic conditions, stability of four fixed dose combination may be affected. The instability includes changes in drug strength, gain in moisture, and change in dissolution profile and increase in degradation products (Saranjit et al., 2006). Patients issued with sub-standard drugs, could experience the following conditions according to MSH/WHO (1997) and Laserson et al. (2000).

i. Lack of curative power leading to death or prolonged illness.

ii. Toxic and adverse reactions in case the drug has expired or exposed to adverse climatic conditions like excessive heat or humidity.

iii. Increased cost of treatment due to development of drug resistance.
iv. Treatment failures as well as drug resistance to *Mycobacterium tuberculosis* organisms.

1.3 Study Justification

Regular post marketing surveillance for pharmaceuticals in Kenya is poor or non-effective and the risk for poor quality drugs finding their way into the public health care system is real. (PPB 2010, PPB 2011) Batch to batch analysis at the point of entry does not exist, thus poor quality drugs may find their way into the country. In this study, pharmaceutical factors affecting the quality of four fixed dose combination anti-TB drugs were assessed and documented especially the effects of transportation, packaging and storage conditions in health facilities. The report findings will be used by the Government to provide appropriate interventions in the manufacture, procurement, distribution, storage and use of anti-TB drugs.

1.4 Research Questions

i. What is the compliance of the four fixed dose combination anti-TB drugs with the International Pharmacopoeia standards?

ii. What are the differences in quality between the sampled four fixed dose combination anti-TB drugs in KEMSA and Health facilities?

iii. What are the storage conditions in KEMSA and the health facilities?
1.5 Hypothesis

The quality of four fixed dose combination anti-TB drug supplied by NLTP to the public health facilities in Coast and Nairobi counties does not meet the International Pharmacopoeia standards.

1.6 General Objective

To assess the quality of four fixed dose combination anti-tuberculosis drug in public health facilities in Mombasa, Kwale, Kilifi and Nairobi Counties in Kenya.

1.7 Specific Objectives

i. To determine the active content (assay), uniformity of weight, friability, and dissolution of the Fixed Dose Combination anti-TB drugs sampled from Nairobi, Mombasa, Kilifi and Kwale counties.

ii. To compare quality of sampled Fixed Dose Combination anti-TB drugs from health facilities with those sampled from KEMSA

iii. To determine the storage conditions practiced by health facilities for Fixed dose Combination and KEMSA

1.8 Significance and anticipated outcome

The findings of the study will have policy implications for the Kenyan government, especially for the NLTP and the Pharmacy and Poisons Board (PPB). The report findings will be useful as an indicator of the quality and stability of the four fixed dose anti-TB drugs in the health facilities. The study will provide new knowledge because such a study has not been reported in Kenya. It will be necessary to carry out similar studies in other
forty three counties and many drugs per health facility are collected and analyzed. The Regulatory Authority will also use the report findings to influence the Manufacturing Practices of local and foreign manufacturers of anti-TB drugs and in strengthening the post market surveillance of anti-TB drugs and enforcing the guidelines for proper storage of pharmaceutical commodities in public health facilities as well as appropriate packaging.

1.9 Delimitation and Limitation of the study

1.9.1 Delimitation

This study assessed the quality of the four fixed dose anti-TB drugs that are supplied by the NLTP from KEMSA. These are the drugs that are given to TB patients during the first two months of treatment (intensive Phase). The study concentrated on three public health facilities in Mombasa and three health facilities in Nairobi and three sites in KEMSA.

1.9.2 Limitation

The cost of analysis was high and thus limiting sample size and the facilities assessed.

1.10 Conceptual Framework

Storage conditions for pharmaceutical products should be in compliance with the labelling requirements which are established by the manufacturer during manufacture as per the laid down procedures in the WHO, Good Manufacturing Practices (GMP) guidelines. The stability of active ingredients is affected by the way it is formulated, packaged and transported to health facilities. The drug must retain its properties within specified limits in order to be useful. Storage conditions for example, heat and humidity
can lead to physical deterioration and chemical decomposition, reduced potency, and formation of toxic by-products of degradation. This is more likely to occur under tropical conditions of high ambient temperature and humidity (UNHCR, 2006). Packaging should be able to protect the formulation during transportation and storage. The following is a diagrammatical representation of the relationship of dependent (quality of the drug) and independent variables (heat, humidity light, transportation and packaging). The outcome of optimal storage conditions, transportation and packaging is quality of drug ensured and thus effectiveness of the anti-TB dug (Figure 1.1).
Quality
- Active ingredient
- Formulation

Transportation
Packaging

Storage conditions
- heat
- humidity
- light

Effectiveness of anti-TB drugs

Figure 1.1: Conceptual framework of the study
2.1 Tuberculosis

2.1.1 Aetiology of Tuberculosis

Tuberculosis (TB) is a highly contagious disease caused by a bacterium known as *Mycobacterium tuberculosis*. The disease generally affects the lungs, but it also can invade other organs of the body, like the brain, kidneys and lymphatic system. Extra pulmonary tuberculosis is less common than pulmonary tuberculosis but is usually more difficult to diagnose. Diagnosis usually requires invasive procedures or biopsies. More than 50 species of the genus *Mycobacterium* are now recognized as potential human pathogens and are now called simply “non-tuberculous mycobacteria” (NTM). Examples of this mycobacterium are *M. avium*, *M. bovis*, *M. fortuitum*, *M. chelonei*, *M. ulcerans*, and *M. abscessus*. *M. marinum* (WHO, 2008).

2.1.2 Tuberculosis Epidemiology and Spread of Tuberculosis

Roughly one-third of the world's population has been infected with *M. tuberculosis*, and new infections occur at a rate of one per second. However, not all infections with *M. tuberculosis* cause tuberculosis disease and many infections are asymptomatic. In 2007 there were an estimated 13.7 million chronic active cases and in 2010 there were 8.8 million new cases, and 1.45 million deaths, mostly in developing countries. 0.35 Million of these deaths occur in those co-infected with HIV. Tuberculosis is the second most common cause of death from infectious disease (after HIV) The absolute number of tuberculosis cases has been decreasing since 2005 and new cases since 2002 .China has achieved particularly dramatic progress, with an 80 percent decline in its TB mortality
rate. The distribution of tuberculosis is not uniform across the globe; about 80% of the population in many Asian and African countries test positive in tuberculin tests, while only 5–10% of the U.S. population test positive. In 2007, the country with the highest estimated incidence rate of TB was Swaziland with 1200 cases per 100,000 people. India had the largest total incidence, with an estimated 2.0 million new cases. In developed countries, tuberculosis is less common and is mainly an urban disease. The incidence of TB varies with age. In Africa, TB primarily affects adolescents and young adults. However, in countries where TB has gone from high to low incidence, such as the United States, TB is mainly a disease of older people, or of the immuno-compromised (WHO, 2009).

Tuberculosis is spread by airborne contamination, through coughing, sneezing, and spitting. Only a small amount of inhaled germs are needed to become infective, however prolonged exposure to someone else that has TB is the easiest way to get the disease. Those who have a weakened immune system are even more at risk. The infected droplets are carried through the air and then inhaled by other people. Not everyone who is exposed to TB gets an active infection. Only those who have the actual bacteria in their lungs get sick and are considered infectious (Deborah, 2011).

2.1.3 The burden of Tuberculosis

Tuberculosis has re-emerged as a major public health problem in the world. It is estimated that a third of the world population is infected with tubercle bacillus, with eight (8) million people progressing to active tuberculosis disease each year, 2 million of whom die of the disease. The WHO reported that incidence of TB grew by 1% globally
in the year 2003 even though the incidence fell or was stable in five out of six WHO regions. In 2003 the African region witnessed a sharp rise in the incidence of TB which was attributed to the high HIV prevalence in this region. Of the more than nine million new cases of active TB that occur worldwide each year, a disease that is both curable and preventable, approximately 30% of the patients are in Africa (WHO, 2004). This translates into 363 per 100,000 persons in Africa each year being newly infected with TB. Twenty-two countries designated as having a high-burden of TB by the World Health Organization account for 80% of the world’s TB cases; nine are in Africa (Democratic Republic of Congo, Ethiopia, Kenya, Mozambique, Nigeria, South Africa, Tanzania, Uganda, and Zimbabwe).

The most TB-affected part of Africa is Southern Africa, with the disease also cutting a deadly swath through East and Central Africa. A few West African countries also bear a large TB burden while most North African countries are relatively less affected. In most cases, a heavy TB burden goes hand-in-hand with a high HIV prevalence. In Africa, TB is often the first manifestation of HIV infection, and it is the leading cause of death among HIV-infected individuals.

Kenya is one of the 22 high TB burdened countries in the world which collectively contribute 80% of the global TB disease burden. Kenya is experiencing a generalized TB epidemic affecting the young economically productive age groups (15-44 year old). Males are 1.4 times more likely to have TB than females. In 2004 a total of 106,000 cases of TB were notified to the National Leprosy and Tuberculosis Programme (NLTP) which represents a TB case notification rate of 320 per 100,000 populations. Since the
early nineties, TB cases have increased almost ten-fold, mainly due to the HIV/AIDS epidemic. People Living with HIV/AIDS (PLWHA) are the major subgroup with increased incidence of tuberculosis. In 1994 a national survey to determine the prevalence of HIV among TB patients found that 40% of TB patients were HIV sero-positive. It is currently estimated that over 60% of TB patients are co-infected with HIV/AIDS (NLTP, 2006).

2.1.4 Tuberculosis and HIV/AIDS

It is a fact that HIV/AIDS influences tuberculosis in several ways as the virus is the most potent known risk factor for reactivation of dormant infection. Individuals infected with HIV/AIDS, the tubercle bacilli have an annual risk of disease of 5-10% as opposed to non-HIV infected individuals who have a similar risk but over a life time. About one in two to three persons infected with both TB and HIV will have TB in their lifetime. The HIV/AIDS increases the rate of progression of new TB infections to disease and also increases the risk of recurrence of previously successfully treated disease. In 2005 it was estimated that more than 60% of TB patients in Kenya were HIV infected. Similarly HIV infected TB patients are more likely to develop other acute infections and be hospitalized while receiving TB treatment. Some of these infections include bacteremic Streptococcal pneumonia and Non-typhi Salmonella septicemia. Additionally, HIV infected TB patients are more likely to die while receiving TB treatment than TB patients who are not HIV infected. Early deaths in HIV infected TB patients may be due to TB itself and related to late diagnosis of the TB while late deaths are usually due to non-TB HIV related infections (NLTP, 2006).
2.1.5 Prophylaxis of Tuberculosis

TB prevention consists of two main parts. The first part of TB prevention is to stop the transmission of TB from one adult to another. This is done through firstly, identifying people with active TB, and then curing them through the provision of four fixed dose drug treatment. With proper TB treatment someone with active TB disease will very quickly not be infectious within two months of treatment and so can no longer spread the disease to others. The second main part of TB prevention is to prevent people with latent TB from developing active, and infectious, TB disease by mass screening and treatment.

There is a vaccine for TB, called Bacillus Calmette-Guerin (BCG) but it makes only a small contribution to TB prevention, as it does little to interrupt the transmission of TB among adults. The BCG vaccine has been shown to provide children with excellent protection against the disseminated forms of TB; however protection against pulmonary TB in adults is variable. Since most transmission originates from adult cases of pulmonary TB, the BCG vaccine is generally used to protect children, rather than to interrupt transmission amongst adults. World Health Organization (WHO) recommends that Isoniazid should be taken daily for at least six months and preferably nine months. Isoniazid is in a similar way to the use of the BCG vaccine, it is mainly used to protect individuals rather than to interrupt transmission between adults (WHO, 2009).

2.1.6 Control of Tuberculosis

Tuberculosis control in the country is based on the elements of the WHO strategy of Directly Observed Treatment Short Course (DOTS) which has been found to be the most
cost effective intervention for the control of TB. The DOTS strategy has the following components:

i. Political commitment to provide adequate human, financial and other resources for sustained TB control,

ii. Case finding with a focus on detection of the most infectious cases through a network of quality assured sputum smear microscopy services,

iii. Standardized short-course regimens with direct observation of drug intake at least in the initial phase of treatment of TB,

iv. Regular and uninterrupted supply of quality anti-TB drugs,

v. A standardized recording and reporting system that ensures that all detected cases are reported and treatment outcomes of every reported case determined (NLTP, 2006).

2.1.7.1 Treatment of Tuberculosis using Fixed Dose Combination

Tuberculosis treatment involves the use of multiple drugs taken in combination. This treatment is done to prevent the emergence of drug resistance to any of the drugs. When single drugs are used (monotherapy) the tubercle bacilli quickly develop resistance to the drug used. For this reason anti-TB drugs should always be used in combination and currently most anti-TB drugs are available as tablets containing multiple drugs in Fixed Dose Combinations (FDC). There are five primary drugs used to treat TB: Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E) and Streptomycin (S).

In the first two months of treatment four drugs are used to rapidly reduce the number of tubercle bacilli (bacillary load) in the body. This phase is called the Intensive phase of TB
treatment. After two months, two drugs are used for 4-6 months and this phase is called the Continuation Phase of TB treatment.

Anti-TB drugs should be taken in the right combinations, with the right doses and the correct schedules for the appropriate duration. To promote total adherence to treatment an individualized patient centered approach should be developed. Therefore Direct Observation of Treatment (DOT) should be promoted using a treatment supporter who is acceptable and accountable to the patient and to the health system. This treatment supporter could be a health care worker, a family member or a community volunteer and the DOT may take place at home, workplace, health facility or other convenient place agreeable to the patient, the treatment supporter and the health care system (NLTP, 2006).

2.1.7.2 Anti-TB Drug Adverse Effects

While most patients treated for TB experience no problems with the treatment, a few patients may have significant side effects which can threaten life or interfere with the quality of life. All health care workers managing cases of TB should be familiar with the common side effects of anti-TB drugs and how to manage these side effects. The following are some of the common side effects of anti-TB drugs indicated.

i. Isoniazid: Peripheral neuropathy and hepatitis.

ii. Rifampicin: Gastrointestinal side effects including anorexia, and vomiting, hepatitis nausea and will reduce effectiveness of oral contraceptive pill.

iii. Pyrazinamide: Joint pains and hepatitis.

iv. Ethambutol: Eye damage (optic neuropathy).
Any of these drugs may cause a skin rash. Tuberculosis patients who are HIV infected patients may experience more severe side effects. (NLTP, 2005)

2.1.8 Drug resistance to Mycobacterium tuberculosis

Antimicrobial resistance is also known as drug resistance and occurs when microorganisms such as bacteria, viruses, fungi and parasites change in ways that render the medications used to cure the infections they cause ineffective. This is a major concern because a resistant infection may kill, can spread to others, and impose huge costs to individuals and society (WHO, 2000). Global surveillance has shown that drug resistant tuberculosis is widespread and is now a threat to tuberculosis control programs in many countries.

The advent of HIV/AIDS in the 1980s resulted in an increase in transmission of TB associated with outbreaks of multidrug-resistant TB (MDR-TB), which is resistant to Isoniazid (I) and Rifampicin(R). Extensively drug-resistant TB (XDR-TB) is defined as TB with resistance to at least Isoniazid and Rifampicin and resistance to a fluroquinolone and a second line injectable agent (like amikacin, kanamycin or capreomycin). (WHO, 2008). In the early 1980s drug resistance surveillance was resumed in developed countries, but the true incidence remained unclear in the developing world. The most effective means to prevent the emergence of drug resistance is by implementing the (DOTS). (WHO, 2003).
2.2 Quality Assessment of anti-TB drugs

Factors affecting quality of anti-TB drugs include formulation, packaging, storage and humidity.

2.2.1 Formulation

Good manufacturing practice (GMP) is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. The GMP is aimed primarily at diminishing the risks inherent in any pharmaceutical production, which may broadly be categorized in two groups: cross contamination/mix-ups and false labeling.

Above all, manufacturers must not place patients at risk due to inadequate safety, quality or efficacy; for this reason, risk assessment has come to play an important role in WHO technical report series of 2003. The bioequivalence of FDCs is sensitive to changes in the production process. The supplier is consequently required to submit a declaration that,

Since the last Rifampicin bioequivalence test done,

i. The same raw materials are still being used

ii. No changes have been made in the production process

iii. Dissolution tests have been performed on each consecutive batch – following the first test for which the bioequivalence test was performed and the results were satisfactory (if required, results of these tests must be provided by the supplier).

Manufacturers or suppliers are advised that tests may be carried out on a sample taken from any of the batches supplied under the current contract (IUATLD, 2001).


2.2.2 Packaging of anti-TB drugs

In the framework of the Stop TB Initiative, a “Global Drug Facility” (GDF) was created in 2001 to provide anti-tuberculosis drugs for some countries, including Kenya, using suppliers whose products are of proven quality through pre-qualification by WHO/IUATLD, 2001). The GDF uses user-friendly packaging which is health worker and patient focused. The packaging include, specially designed blister sheets and individual Patient Kits (containing a full course of treatment) to protect the contents against damage and humidity (GDF).

2.2.3 Storage of anti-TB drugs

Maintaining proper storage conditions for health commodities is vital to ensuring their quality. Product expiration dates are based on ideal storage conditions and protecting product quality until their expiration date is important for serving clients and conserving resources (WHO/DELIVER, 2003). Anti-TB drugs must be stored in optimal conditions for the reason that substandard and deteriorated drugs are a serious problem for the tuberculosis control. Drugs should not be stored under direct sunlight or, under moist environment. Also stocks of drugs should be arranged by putting shortest expiry date in the front, to avoid loss due to expiry and possible dispensing of a deteriorated drug to a patient. The first-expired first-out (FEFO) and then the first-in first-out (FIFO) principles should apply (WHO, 2002). Ethambutol in the combination for example has been shown to draw moisture due to its hygroscopic nature, thereby creating a liquid environment good for degradation of the drug in combination (Kenyon et al., 1999).
2.2.4 Monitoring Humidity

Hydro thermometers are used in drug stores to monitor humidity. The record of humidity should be maintained in charts and checked on a daily basis by the concerned Store person and corrective measures taken as necessary.

**Control of Humidity:** In order to keep humidity levels below the maximum 65% RH as recommended for storage of drugs, following measures may be taken:

i) **Ventilation:** Windows or air vents of the store are opened to allow air circulation or fans are used to circulate fresh air from outside.

ii) **Protection from Sunlight:** To protect the drugs from sunlight, the following measures may be taken by ensuring that, windows are shaded or curtains are used if in direct sunlight, products are kept in cartons/drug boxes, and that the products are not stored or packed in sunlight.

iii) **Control of temperature:** The Anti-TB Drugs should preferably be stored below 25°C, in the area specified for storing the anti-TB drugs, which should be at least 10cm off the floor and 30 cm away from the walls and other stacks. Experimental data/literature review reveals that these drugs lose their efficacy beyond six months if exposed to stressful storage conditions of 40°C temperature and humidity of 75% + 5% RH (DG of Health Services, 2011).

2.3 Global quality concerns of anti-TB drugs

Serious concerns have been raised in several studies done on the use of the four fixed dose combinations due to quality problem. It was observed that one in every three FDC containing Rifampicin and Isoniazid had lower than the required strength of Rifampicin. Explanation given is that significant loss of Rifampicin occurs before absorption due to
formation of 3-formylrifamycin which further reacts with Isoniazid to form isonicotinyl hydrazone (HYD). Hydrazone then converts back to Isoniazid and an insoluble and poorly absorbed 3-formyl rifamycin SV (3-FRSV), resulting in the recovery of Isoniazid but causing the loss of Rifampicin. The other explanation given as to the instability of FDC is that due to absorption of moisture by Ethambutol one of the drug constituent, creating an acidic hydrolytic environment thus accelerates the reaction between Rifampicin and Isoniazid (Saranjit et al., 2006).

Bioavailability of Rifampicin is significantly impaired when it is administered along with Isoniazid as a FDC, in comparison with administration of formulation containing only Rifampicin (Shishoo et al., 2001; Immanuel et al., 2003). An almost 30% fall in bioavailability of Rifampicin has been reported on administration of Rifampicin Isoniazid FDC. The drop of bioavailability of Rifampicin from FDC products has been attributed to a facile drug-drug reaction between Rifampicin and Isoniazid in the acidic medium of stomach, whereby significant loss of drug occurs before absorption.

2.4 Tuberculosis treatment targets

According to a WHO report, (2004) on Global Tuberculosis Control, the set targets of 70/85 were not reached by end of 2000 and therefore the targets were reset to 2005. In the same report, it was reported that treatment success under DOTS for the year 2001 was 82% on average among the 201 countries that reported to WHO. Treatment success was 71% in WHO African Region and 70% in Eastern Europe. The explanation given to the low treatment success was due to complications of HIV co-infection and drug resistance (WHO, 2004). Tuberculosis is a major cause of morbidity and mortality in the world. The
disease has re-emerged as a major public health problem in the world. World Health Organization has estimated that a third of the world population is infected with TB and over 3 million people die from TB (Crofton et al., 1992). It has been reported that TB cases in Kenya have increased from 11,625 in 1990 to 108,401 cases in 2005 (NLTP, 2005). It is important therefore to maintain the quality of FDCs anti-TB drugs in order to minimize the treatment of TB failures and poor treatment outcomes. The purpose of quality assurance is to ensure that each drug reaching the patient is safe, effective and of high quality (UNHCR, 2006). One of the elements of DOTS is to have uninterrupted and sustained supply of quality-assured anti-TB drugs which are fundamental to the control of TB. For this purpose, an effective drug supply and management system is essential. A reliable system of procurement and distribution of all essential anti-TB drugs to all relevant health facilities should be in place (MSH, 2005).

In a study done on the Substandard Tuberculosis drugs in the global market, it was found out that 21% of FDC were substandard (Laserson et al. 2001). It was noted that poor quality anti-TB drugs have a potential in creating drug resistant Mycobacterium tuberculosis. The global prevalence of sub-standard anti-tuberculosis has not been systematically assessed. Usually TB programs are precisely the places where quality assurance laboratory facilities are less accessible or available to test for counterfeit and substandard anti-TB drugs (Laserson et al., 2001).

An essential element of effective tuberculosis control is a reliable supply of good quality drugs provided to patients freely. The FDCs incorporating two or more anti-TB drugs into one tablet in fixed proportions, have been used since the late 1980s and are registered in more than 40 countries. The WHO model list of essential drugs of 2005 includes FDCs
in specific formulations. Potential advantages of FDCs include: the use of FDCs involves fewer products and will result in more accurate prescribing practices by clinicians and adherence by the patients; procurement, management, and distribution of drugs are simplified by the use of FDCs; potential disadvantages of FDCs include: bioavailability (the amount of an ingested drug absorbed and reaching into the blood) of Rifampicin may decrease when it is combined with other drugs in the combination; use of FDCs particularly in three and four drug combinations, could therefore result in lower plasma levels of Rifampicin, with consequent treatment failures, relapses, and/or emergence of Rifampicin-resistant strains of *Mycobacterium tuberculosis*. Although there may be proven bioavailability during the approval or tender process, there is often no systematic mechanism to ensure that all subsequent batches of FDCs also have adequate bioavailability. The regulatory structures required to adequately monitor GMP and ensure bioavailability standards for FDCs (either imported or local) should be strengthened (Toman’s/WHO, 2004). According to (WHO, 2001) report, tuberculosis kills over 250,000 children worldwide and is the leading infectious cause of death among young women. The HIV/AIDS pandemic are fuelling an explosive growth of new TB & HIV cases. TB is the leading killer of people with HIV (WHO, 2001).

### 2.5 WHO definition of a substandard drug

The World Health Organization (WHO) defines a substandard product as “a product with genuine packaging with incorrect quantity of ingredient (not deliberate).” That is a legally branded or generic product, but one that does not meet international standards for quality, purity, strength, or packaging. Taking into consideration that TB is a global emergency, quality TB drugs must be assured. A study conducted on the quality
assessment of four fixed-dose combination tuberculosis drugs using thin-layer chromatography by Kenyon et al. (1999) found out that out of a convenient sample of 13, 4/13, (31%) of the FDCs were substandard. These included 2/13, (15%) with low Rifampicin content, 1/13, (8%) had excessive Pyrazinamide, 1/13, (8%) of the samples had excessive Rifampicin. A substandard product may contain no active ingredient, harmless inactive ingredients and may be unregistered in the country where it is sold, or have been manufactured illegally, or smuggled into the country and thus be on sale illegally; Some drug regulatory agency may lack skill and/or resources to properly evaluate product dossiers); the product may also pass of expiry (USP/ QDI, 2003).

2.6 Drug quality concerns in developing countries

Sub-standard medicines are a problem in both developed and developing countries, the World Health Organization (WHO) estimates that up to 25% of the medicines used in developing countries are counterfeit or sub-standard. In developing countries, medicines used to treat life-threatening conditions such as Malaria, TB and HIV/AIDS are commonly found to be counterfeit (ICN, 2005). A study conducted in India and Vietnam by U.S. Centers for Disease Control and Prevention (CDC) on a total of 71 anti-TB drugs, samples of Isoniazid and Rifampicin as single or fixed dose combination (FDC) showed 13% Rifampicin containing products were sub-standard, containing less than 85% of stated content. More FDCs, 21% versus single drug samples, 13% were substandard (USP/ QDI, 2003).
2.7 Drug quality concerns in Kenya

Studies done in the Drug Analysis and Research Unit (DARU), University of Nairobi, between 1996 and 2000 of various pharmaceutical products indicate that failure rate of drugs that were analyzed is 24.6%. The study also showed that the quality of drugs in the market varies with the type of the drug and the manufacturer, whether local or foreign (Thoithi et al., 2002). A post market surveillance of first line anti-Tuberculosis medicines was conducted in Kenya in 2010 indicated that 78% of the sites had appropriate storage conditions while percentage humidity ranged from 33-62%, there was however significant differences in humidity across the sites. From the laboratory results of the 120 product sample analyzed, 10 failed to comply with one or more of the test parameters, representing 8.3% failure rate. All the non-compliant products were 2 component FDC samples with Rifampicin and Isoniazid combination accounting for 80% of non-compliance and the Ethambutol and Isoniazid combination accounting for the remaining 20% of failures (PPB/MOH, 2010).
CHAPTER THREE: METHODOLOGY AND RESEARCH DESIGN

3.1 Study Areas

This study was carried out in Nairobi, Mombasa, Kwale and Kilifi counties as shown in the maps in Appendix 1a and 1b. Coast Counties were chosen because of the hot and humid climatic conditions. Over the course of a year, the temperature at the coast typically varies from 21°C to 33°C and is rarely below 20°C or above 34°C. The average relative humidity is 73%. The normal storage conditions of drugs are dry, well lit, ventilated premises at a temperature of 15-30°C and a Relative Humidity of 60%. Nairobi County was chosen because it has a moderate climate and an average temperature of 19°C that are ideal for storing pharmaceuticals. Sampled drugs were packed in cartons containing strips, each strip containing either twenty eight or twenty four tablets. The number of strips ranged from four, eight and ten per carton thus 4x28, 8x28 and 10x28.

In Nairobi County, samples was collected at,

i. KEMSA: Three samples from three different locations in the warehouse, at the front (F), 8x28(224) tablets were sampled, Center(C) 4x28(112) tablets were sampled and the back (B), 4x28(112) tablets were sampled.

ii. Rhodes Chest Clinic, where 4x28(112) tablets were sampled.

iii. District Store Casino, where 4x28(112) tablets were sampled.

In Mombasa, Kwale and Kilifi counties, drug samples were collected in the following facilities;

i. Kisauni Health Center: This facility is based in Mombasa district (Mombasa County) and 8x28(224) tablets were sampled
ii. Diani Health Center this facility is in Kwale district (Kwale County) and 10x24(240) tablets were sampled.

iii. Kombeni Dispensary this facility is in Kilifi district (Kilifi County) and 8x28(224) tablets were sampled.

The actual details of the health facilities, the number of drug samples collected and the drug sample manufacturers are indicated in Table 3.1 and 3.2

**Table 3.1: Sampled facilities and Number of tablets**

<table>
<thead>
<tr>
<th>Facility name</th>
<th>Sample quantity</th>
<th>Number of tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kisauni HC</td>
<td>8x28</td>
<td>224</td>
</tr>
<tr>
<td>Kombeni DISP</td>
<td>8x28</td>
<td>224</td>
</tr>
<tr>
<td>Diani HC</td>
<td>10x24</td>
<td>240</td>
</tr>
<tr>
<td>Rhodes HC</td>
<td>4x28</td>
<td>112</td>
</tr>
<tr>
<td>Casino Store</td>
<td>4x28</td>
<td>112</td>
</tr>
<tr>
<td>KEMSA F</td>
<td>8x28</td>
<td>224</td>
</tr>
<tr>
<td>KEMSA C</td>
<td>4x28</td>
<td>112</td>
</tr>
<tr>
<td>KEMSA B</td>
<td>4x28</td>
<td>112</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>1360</strong></td>
</tr>
</tbody>
</table>

**Table 3.2 Number of sampled tablets by manufacturer**

The table below shows the name of the manufacturer of the drug samples and the number of tablets that were randomly sampled from the facilities.

<table>
<thead>
<tr>
<th>Name of Manufacturer</th>
<th>No.of facilities</th>
<th>No. of Tablets sampled and %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupin Ltd India</td>
<td>1(12.5)</td>
<td>112(8.2)</td>
</tr>
<tr>
<td>Macleods Pharmaceuticals</td>
<td>2(25.0)</td>
<td>352(25.9)</td>
</tr>
<tr>
<td>Svizera Labs India</td>
<td>5(62.5)</td>
<td>896(65.9)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>8</strong></td>
<td><strong>1360</strong></td>
</tr>
</tbody>
</table>
3.2 Study Population

The study consisted of analysis of four fixed dose combination of anti-TB drugs that are procured, stored in Kenya Medical supplies Agency (KEMSA) and those distributed by the National Leprosy Tuberculosis Programme (NLTP) to health facilities.

3.3 Study Design

A cross Sectional survey was conducted in this study where samples of four fixed dose combination FDCs anti-TB drugs under different climatic conditions were purposively collected from eight public health facilities. The samples were analyzed in the National Quality Control Laboratory (NQCL) for assay using HPLC, for dissolution using a dissolution tester machine, for friability using friability machine and for uniformity of weight using a Sartorius balance. National Quality Control Laboratory (NQCL) is a laboratory that is pre-qualified by WHO. The United States Pharmacopoeia (USP) 2006 specifications were used. These specifications are:

i. assay limits 90-110% of the stated label claim,

ii. Dissolution: no tablet should be less than 80% of the amount released in 45 minutes.

iii. Friability: A maximum weight loss of not more than 1% of the weight of the tablets being tested,

iv. Uniformity of weight: Not more than two tablets should deviate by more than 5% from the mean.
3.4 Variables

3.4.1 Dependent variable

The dependent variable was the quality of the four fixed dose combination anti-TB drugs supplied by NLTP. According to (MSH/WHO, 1997) drug quality may be affected by a number of factors described as independent variables.

3.4.2 Independent Variables

The factors that affect the quality of the four fixed anti-TB drug, some of which were assessed are temperature, humidity, excessive light and transportation.

3.5 Target Units of Study

The target units of study were the four fixed dose combination anti-TB drugs that the NLTP supplies to health facilities in Coast and Nairobi Counties.

Study Units: Anti-TB drugs supplied by NLTP to different health facilities in Coast and Nairobi Counties.

3.6 Inclusion Criteria

Anti-TB drug distributed by NLTP in four fixed dose combination in the original packaging from KEMSA to public health facilities

3.7 Exclusion Criteria

Anti-TB drugs not supplied by NLTP were excluded from the study, so was four fixed dose combination anti-TB drug that had seals broken off in the health facility or the container had not been sealed and protected from excessive light. Also excluded from the
study were four fixed dose combination anti-TB drugs that were not found in the health facility and four fixed dose combination anti-TB drugs that were expired

3.8 Sampling Techniques

The counties of Mombasa, Kilifi, Kwale and Nairobi were purposively selected. The coastal regional counties have extreme climatic conditions. Over the course of a year, the temperature at the coast typically varies from 21°C to 33°C and is rarely below 20°C or above 34°C. The average relative humidity is 73%. Nairobi has a fairly moderate climate. The temperature in Nairobi peaks at 25°C. Three health facilities in the coastal region and five facilities in Nairobi County were purposively selected while samples from different batches were randomly selected. The sample was conveniently selected from the Ministry of Health essential drug list of 2003, where the FDCs are listed. In each facility, random sampling of batches was done.

3.9 Sample Size Determination

The sample size was calculated using the formula by Fisher et al. 1998) for determining sample size when the population is greater than 10,000.

The assay, dissolution, friability, uniformity of weight tests of each combination drug were carried out, as per United States Pharmacopeia (USP) specifications, 2006. Fifty tablets of the combination drug were required for various tests. The fifty tablets were randomly sampled from the samples (1360) that were randomly sampled from each of the eight health facilities, making a total of four hundred tablets. Table 3.1 shows that the total tablets sampled were 1360 from the eight facilities. The minimum tablets that could have been sampled were a pack of either 4x28, 8x24 or 10x24 tablets. Each strip of the drug contained either 28, 24, tablets.
The formula as used by Fisher et al. (1998) was used to determine the sample size.

\[ n = \frac{Z^2 Q D}{d^2} \]

where, 

- \( n \) = the desired sample size (if the target Units population is greater than 10,000)
- \( Z \) = the standard normal deviate, (1.96) which corresponds to the 95% Confidence Interval
- \( P \) = Failure rate of various drugs analyzed between 1996-2000 was found to be 24.6 % (Thoithi et al., 2002)
- \( Q = 1 - P \)
- \( D \) = the design effect, which is usually 1
- \( d \) = the degree of accuracy = 0.05

Thus, \( n = \frac{1.96^2 \times 0.25 \times 0.75 \times 1}{0.05} = 300 \) tablets.

The samples taken to the laboratory was 400 tablets.

The number of tablets sampled randomly from the eight facilities is shown in Table 3.1

The tablets sampled were packed in 8x24 in three facilities, 10x24 in one facility and 4x28 in four facilities. Total number of tablets in all the cartons was 1360.

### 3.10 Research Instruments

Observation check list was used as per the appendices. Assay, dissolution, friability and uniformity of weight of the FDCs was performed by the National Quality Control Laboratory which is WHO pre-qualified laboratory meaning that it is fully equipped to perform the requested analyses. The researcher made laboratory request using the already designed request forms. The internationally set standards in the USP, 2006, using the HPLC were used. Certificates of analysis were issued and the results recorded using the laboratory forms.
3.11 Validity

Validity of the instruments was ensured through regular calibration by the Kenya Bureau of Standards (KEBS) and the use of reference standards to validate the analytical results. Data quality was assured by the researcher’s personal involvement in sample collection and analysis of all the samples.

3.12 Data Collection Method

Data collection from the health facilities was done through an observation check list. The checklist was used to put down details of the sample that were collected from health facilities to be analyzed at the NQCL (Appendix 2). After the analysis, the products were given certificate of analysis (Appendix 3). The following tests were done at the NQCL according to USP, 2006 specifications.

3.12.1 Uniformity of weight

Uniformity of weight is defined as the degree of uniformity in the amount of the drug substance among dosage units such as tablets used in this study. This is demonstrated by weight variation expressed as Relative Standard Deviation (RSD).

Procedure: Twenty tablets of the four fixed dose combination were taken randomly and individual weights taken using a Sartorius Basic BA 2105 weighing balance which has a weighing range of 100 mg to 200 mg, and then the average weight was determined. Relative Standard Deviation (RSD) was calculated by subtracting individual weight from the average weight, multiplied by 100 and divided by the average weight to establish whether formulation was correct in terms of specified weight of active ingredients, on the
label which is Isoniazid 75mg, Rifampicin 150mg Pyrazinamide 400mg and 275mg Ethambutol.

3.12.2 Friability

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is measured by the use of friability tester. Twenty tablets were weighed and placed in the friability apparatus where they are exposed to rolling by rotating the apparatus with the tablets. The repeated tablets shocks as they fall 6 inches in each turn within the friability apparatus for four minutes was done. After four minutes of this treatment or 100 revolutions, the friability apparatus is stopped, the tablets were cleaned off any chipped particles, weighed and the weight compared with the initial weight. The percentage weight loss was calculated using the following formula:

\[
\text{Weight before testing} = (x) \text{ g}
\]

\[
\text{Weight after testing} = (y) \text{ g}
\]

\[
\text{Weight lost} = (x-y) \text{ g}
\]

\[
\text{Percentage weight lost} = \frac{(x-y) \text{ g} \times 100}{(x) \text{ g}}
\]

The loss due to abrasion is a measure of tablet friability. The % weight loss should not be more than 1%.

3.12.3 Dissolution

This was done by using the dissolution tester, ERWEKA DT 700HH serial number 118376 for 45 minutes to determine the amount of active ingredient that is available for
absorption and results recorded in minutes as per analytical methods given below. Methods described in USP edition 2009 was used in determining dissolution for Rifampicin, Isoniazid, Pyrazinamide and Ethambutol combination. The dissolution tester was used in NQCL branded as Erweka DT 700 HH. Medium: 10 mM pH 6.8 Sodium phosphate buffer was prepared by dissolving 7 g of anhydrous dibasic sodium phosphate in 5 litres of water, and adjusting with phosphoric acid to a pH of 6.8. 900 ml was used in each of the dissolution vessels. They were all six vessels. The USP apparatus 2 is called rotating paddle apparatus and was used at 100 revolutions per minute (rpm) for 45 minutes.

Procedure – Amounts of Rifampicin (C_{43}H_{58}N_{4}O_{12}), Isoniazid (C_{6}H_{7}N_{3}O), Pyrazinamide (C_{5}H_{5}N_{3}O), and Ethambutol hydrochloride (C_{10}H_{24}N_{2}O_{2}.2HCL) dissolved in the medium were determined by withdrawing 10ml which was filtered and injected into the HPLC machine for determination of the amounts of Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol. Not less than 80 % of the labeled amounts of Rifampicin (C_{43}H_{58}N_{4}O_{12}), Isoniazid (C_{6}H_{7}N_{3}O), Pyrazinamide (C_{5}H_{5}N_{3}O), and Ethambutol hydrochloride (C_{10}H_{24}N_{2}O_{2}.2HCL) are dissolved in 45 Minutes

3.12.4 Assay for determination of active Ingredients

This is the main measure of quality. High power Liquid Chromatography (HPLC) apparatus was used to determine the amount of active ingredient which is expressed as a percentage of the label claim (90-110%). Sample preparation and assay for FDCs anti-TB drugs was performed according to USP, 2006 specifications as shown below:
3.12.4.1 Method of assay for Rifampicin, Isoniazid, and Pyrazinamide

Buffer solution – About 1.4 of anhydrous dibasic sodium phosphate was dissolved in 1 L of water, and pH adjusted to 6.8 with phosphoric acid. Mobile phase A – Mixture of Buffer solution and Acetonitrile (94:4). Mobile phase B – Mixture of Buffer solution and Acetonitrile (45:55).

Analysis Mobile phase – Variable mixtures of Mobile phase A and Mobile phase B were used as shown in table 3.3.

Table 3.3: Mobile phase

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
<th>Elution</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
<td>Equilibration</td>
</tr>
<tr>
<td>0 – 5</td>
<td>100</td>
<td>0</td>
<td>Isocratic</td>
</tr>
<tr>
<td>5 – 6</td>
<td>100 → 0</td>
<td>0 → 100</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>6 – 15</td>
<td>0</td>
<td>100</td>
<td>Isocratic</td>
</tr>
</tbody>
</table>

Standard preparation – Accurate weight quantities of Rifampicin Reference Standard, Isoniazid Reference Standard, and Pyrazinamide Reference Standard were dissolved in a mixture of Buffer solution and methanol (96:4) so as to obtain a solution having known concentration of about 0.16 mg per mL, 0.08 mg per mL, and 0.43 mg per mL, respectively.

Assay preparation: Twenty tablets were weighed and finely powdered. Powder equivalent to about 8 mg of isoniazid, was weighed and transferred accurately to a 100 mL volumetric flask in which about 90 mL of Buffer solution added and sonicated for 15 minutes. This was allowed to equilibrate to room temperature, diluted with Buffer Solution to Volume, and mixed.
Chromatographic System – The liquid chromatography was equipped with a 238 – nm detector and a 4.6 – mm x 256 – cm column that contains a 5 - µm base deactivated packing USP L1. (Used BDS Hypersil C18 5 µ 250 mm x 4.6 mm). Flow rate of 1.5 mL per minute was used. Standard preparation was chromatograph peak responses recorded: the relative retention times for Rifampicin, Isoniazid, and Pyrazinamide are about 1.8, 0.7, and 1.0, respectively; the resolution, R, between Isoniazid and Pyrazinamide is not less than 4; the column efficiencies, determined from the Rifampicin, Isoniazid, and pyrazinamide peaks are not less than 24,000 theoretical plates, 4000 theoretical plates, and 5,000 theoretical plates, respectively; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2 %.

Procedure – Equal volumes (about 20 µL) of the Standard preparation and the Assay preparation were separately inject into the chromatograph. Chromatograms recorded and peak responses measured. Quantities, in mg, of Rifampicin (C₄₃H₅₈N₄O₁₂), isoniazid (C₆H₇N₃O), Pyrazinamide (C₅H₅N₃O) in the portion of Tablets taken were calculated by the formula: 100C (rᵤ/rₛ), in which C is the concentration, in mg per ml, of the appropriate Reference Standard in the Standard preparation; and rᵤ and rₛ are the peak responses of the corresponding analyte obtained from the Standard preparation and the Assay preparation, respectively.

**3.12.4.2 Assay for Ethambutol hydrochloride**

Diluents – About 1.4 of anhydrous dibasic sodium phosphate was dissolved in 1 L of water, and pH adjusted to 6.8 with phosphoric acid.

Buffer solution – 1.0 mL of triethylamine and 1 L of water were mixed pH adjusted to 7.0 with phosphoric acid.
Mobile Phase – Mixture of acetonitrile and Buffer solution (50:50).

Standard preparation – Accurate weight quantities of Ethambutol Hydrochloride Reference Standard were dissolved in diluents so as to obtain a solution having a known concentration of about 0.3 mg per ml.

Assay preparation; Twenty tablets were weighed and finely powdered. Powder equivalent to about 30 mg of Ethambutol hydrochloride, was weighed and transferred accurately, to a 100 ml volumetric flask, 90 ml of buffer solution was added and sonicated for 15 minutes, it was allowed to equilibrate to room temperature, diluted with buffer solution to volume, and mixed.

Chromatographic System – The liquid chromatography was equipped with a 200 – nm detector and a 4.6 – mm x 15 – cm column that contains a 5 - µm base deactivated packing USP L10. (Used BDS Hypersil CYANO 5 µ 150 mm x 4.6 mm). Flow rate of 1.0 mL per minute was used. According to the International Pharmacopeia specifications, assay limit is between 90.0 % and 110.0% of the stated label claim.

3.12.5 Analytical procedures

Reagents and solvents Used are, Orthophosphoric acid, Merck Chemicals (Pty) Ltd, Lot No. 1028522, Acetonitrile, Merck. Chemicals (Pty) Ltd, Lot No. 1441830 828, anhydrous dibasic sodium phosphate, Loba Chemie, Lot No. R327405, Triethylamine, Rankem, R066K07, Distilled Water from NQCL. All aqueous solutions used in sample analysis were prepared using purified water obtained through reverse osmosis treatment and ultra filtration through successive 0.45 µm and 0.2 µm membrane filters using a combined Arium 61316 RO and Arium 611 VF water system (Sartorius AG, Gottingen, Germany).
3.12.5.1 Chemical reference standards

Quantitative analyses were carried out using Rifampicin®, Ethambutol (E), Pyrazinamide (Z) and Isoniazid (H) working standards validated against primary chemical reference substances obtained from the United States Pharmacopoeial Convention, Rockville, Maryland, USA.

3.12.5.2 Instrumentation

All masses determined for sample analysis were measured using laboratory analytical balances (Sartorius Basic BA 2105, Germany). Dissolution tests were run using DT 700 HH six-station Dissolution Tester (Erweka, Frankfurt, Germany); The LC apparatus consisted of a Merck Hitachi LaChrom HPLC System (Hitachi Ltd, Tokyo, Japan) incorporating the following components: a quaternary low pressure gradient pump model L7400, a variable wavelength UV detector model L7400, a variable injection volume autosampler model L7200 supported by Merck-Hitachi Model D-7000 Chromatography data station software – HSM Manager Version 4.1 (Merck KgA, Darmstadt, Germany and Hitachi Instruments Inc., San Jose, USA). Mobile phases were degassed using a Sonorex Super RK103H ultrasonic bath (Bandelin Electronic, Berlin, Germany) for 15 min.

3.12.5.3 Chromatographic conditions

Stationary phases used were: Hypersil BDS Cyano 5 μm (250 mm x 4.6 mm ID); Hypersil BDS C18 5μm (250 mm x 4.6 mm ID); Synergi 4 μm C18 (250 mm x 4.6 mm ID). Other chromatographic conditions including mobile phase flow rate, detection
wavelengths, injection volumes and column temperature were set and controlled as described in the relevant monographs.

### 3.12.5.4 Sample Preparation

For assay and dissolution tests, sample and reference standard solutions were prepared as Outlined in the product monographs contained in the United States Pharmacopoeia. Confirmation of identity and quantification of the ingredients in these solutions was subsequently done through HPLC analysis preparation and assay for FDCs anti-TB drugs was performed according to USP, 2006 specifications.

### 3.13 Data Management and Analysis

Data was entered in a MS Access database and analysis done using SPSS software version 11.5. Descriptive statistics was used to organize and summarize collected data and that generated from the NQCL.

### 3.14 Ethical Consideration

Permission to carry out this research was obtained from Kenyatta University’s Graduate School, and the Ministry of Science and Technology. To be able to collect samples from the health facilities, authority was given by Head NLTP and Pharmacy and Poisons Board.
CHAPTER FOUR: RESULTS

4.1 Characteristics of sample population

The four fixed drug combination (FDC) anti-TB drugs composed of Rifampicin 150mg, Isoniazid 75mg, Pyrazinamide 400mg and Ethambutol 275mg in one tablet were sampled from a total of 8 facilities, 3 in Coast counties and 5 in Nairobi County. The facilities in the Coast Counties from which drugs were sampled were two health centers namely Diani in Kwale County, Kisauni in Mombasa County and one dispensary Kombeni in Kilifi County. In Nairobi County, sampling was done from one health center, Rhodes and a district store, Casino as well as from three warehouse locations in KEMSA, the main medical supplies agency in Kenya. In total 1360 tablets were sampled from these facilities and submitted for analysis to the National Quality Control Laboratory, through a laboratory request form. The number of samples taken to the laboratory from Coast County was 688 tablets (50.6%) and from Nairobi County were 672 tablets (49.4%) (Table 3.1). The KEMSA sites from which drugs were sampled represented the point at which drugs are delivered by manufacturers for distribution to health facilities. From the KEMSA sites, a total of 448 tablets representing 32.9% of the total were sampled compared to 912 (67.1%) from health facilities (Table 3.1). All the sampled drugs were Fixed Dose combinations (FDC) containing Rifampicin (R) Isoniazid (H), Pyrazinamide (Z) and Ethambutol (E) and were in tablet dosage form.

The sampled anti-TB drugs originated from three different manufacturers, namely Svizera Labs, Lupin Ltd and Macleods pharmaceuticals. Drugs from Svizera Labs India were distributed in 5(62.5%) of the facilities while those from Macleods and Lupin Ltd were distributed in 2(25%) and 1(12.5%) facilities respectively (Table 3.2). Majority of
sampled tablets 896 (65.9%) were from Svizera Labs, 352(25.9%) from Macleods Pharmaceuticals and 112(8.2%). The type of packaging used in all the drugs was aluminium foil strip packs of either 10 or 28 tablets each and were within the expiry date. All samples were well labeled with batch numbers, manufacturing and expiry dates. Storage condition was indicated as store in a cool, dry place below 25°C and protected from light.

4.2 Compliance of anti-TB FDC drugs with International Pharmacopoeia specifications

Chemical analysis was done at the NQCL and certificates of analysis issued (Appendix 3). The analysis included determination of the active content (assay), uniformity of weight, friability, dissolution of the sampled FDCs anti-TB drugs.

4.2.1 Uniformity of Weight of FDC drugs

The results on uniformity of weight indicate that the analyzed drugs from all eight facilities sampled complied with the uniformity of weight as per the specifications. (Table 4.1).

Table 4.1: Uniformity of weight for Fixed Dose Combination drugs by Facility

<table>
<thead>
<tr>
<th>Facility</th>
<th>N</th>
<th>Deviation of Weight</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kisauni HC</td>
<td>20</td>
<td>None Deviates</td>
<td>Complies</td>
</tr>
<tr>
<td>Kombeni HC</td>
<td>20</td>
<td>None Deviates</td>
<td>Complies</td>
</tr>
<tr>
<td>Diani HC</td>
<td>20</td>
<td>None Deviates</td>
<td>Complies</td>
</tr>
<tr>
<td>Rhodes</td>
<td>20</td>
<td>None Deviates</td>
<td>Complies</td>
</tr>
<tr>
<td>Casino</td>
<td>20</td>
<td>None Deviates</td>
<td>Complies</td>
</tr>
<tr>
<td>KEMSA (F)</td>
<td>20</td>
<td>None Deviates</td>
<td>Complies</td>
</tr>
<tr>
<td>KEMSA (C)</td>
<td>20</td>
<td>None Deviates</td>
<td>Complies</td>
</tr>
<tr>
<td>KEMSA (B)</td>
<td>20</td>
<td>None Deviates</td>
<td>Complies</td>
</tr>
</tbody>
</table>
KEMSA is an expansive government warehouse. To ensure a representative sample, sampling was done from three sections (F) front, (C) Center and (B) Back.

4.2.2 Friability

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling, shipping and road transportation. It is measured using a friability machine. The loss due to abrasion is a measure of the tablet friability. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable according to the specifications in the International Pharmacopoeia (I.P)

Table 4.2 shows the results of friability of sampled drugs. Drugs from seven of the eight facilities (87.5%) complied with friability specifications. The drugs from Diani Health Centre in Kwale, County had a friability of 5.1 thus failed to comply with specifications.

<table>
<thead>
<tr>
<th>Facility</th>
<th>N</th>
<th>Friability</th>
<th>Compliance with friability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kisauni HC</td>
<td>20</td>
<td>0.01</td>
<td>Complies</td>
</tr>
<tr>
<td>Kombeni HC</td>
<td>20</td>
<td>0.01</td>
<td>Complies</td>
</tr>
<tr>
<td>Diani HC</td>
<td>20</td>
<td>5.1</td>
<td>Fail to comply</td>
</tr>
<tr>
<td>Rhodes</td>
<td>20</td>
<td>0.009</td>
<td>Complies</td>
</tr>
<tr>
<td>Casino</td>
<td>20</td>
<td>0.004</td>
<td>Complies</td>
</tr>
<tr>
<td>KEMSA(F)</td>
<td>20</td>
<td>0.005</td>
<td>Complies</td>
</tr>
<tr>
<td>KEMSA(C)</td>
<td>20</td>
<td>0.006</td>
<td>Complies</td>
</tr>
<tr>
<td>KEMSA (B)</td>
<td>20</td>
<td>0.002</td>
<td>Complies</td>
</tr>
</tbody>
</table>

NB. Weight loss of not more than 1% considered acceptable
4.2.3 Dissolution of anti-TB FDC drugs by facility

Dissolution is a standardized method for measuring the rate of drug release from a dosage form into the body system. Table 4.3 shows results of dissolution of Ethambutol in the FDC drugs from each facility. Dissolution ranged from 91.3% for drugs in Diani Health Centre at the Coast to 104% for those at Rhodes health centre in Nairobi.

Dissolution of Rifampicin in the FDC ranged from a minimum of 58.8% in Diani to 96% in Kombeni, both of which are in the Coast. Of the eight facilities, five had their drugs complying with specifications for dissolution of Rifampicin while 3(37.5%), namely Diani, and two from KEMSA (Centre and Back) failed to comply. Although the mean dissolution for Rifampicin from KEMSA C was 80.4%, one tablet had less than 80% dissolution and the specification states that no tablet should be less than 80%. Drugs from KEMSA B also had borderline dissolution of 79.5% indicating that all of the drugs were not above 80% dissolution (Table 4.4).

Table 4.5 shows the results of dissolution of Isoniazid for the sampled drugs from various facilities. Dissolution ranged from 83.7% for drugs from Diani to 94.6% for KEMSA F drugs. Drugs from all the facilities complied with dissolution of Isoniazid.

Drugs from all facilities met the specifications for dissolution for Pyrazinamide as indicated in Table 4.6 with dissolution for Pyrazinamide ranging from a minimum of 92.8% at Rhodes to a maximum of 97.6% at KEMSA F and C.
Table 4. 3: Dissolution of Ethambutol

<table>
<thead>
<tr>
<th>Facility</th>
<th>N</th>
<th>Mean Dissolution (%)</th>
<th>Relative Standard Deviation (RSD)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kisauni HC</td>
<td>6</td>
<td>97.3</td>
<td>2.3</td>
<td>Complies</td>
</tr>
<tr>
<td>Kombeni HC</td>
<td>6</td>
<td>97.1</td>
<td>1.6</td>
<td>Complies</td>
</tr>
<tr>
<td>Diani HC</td>
<td>6</td>
<td>91.3</td>
<td>3.5</td>
<td>Complies</td>
</tr>
<tr>
<td>Rhodes</td>
<td>5</td>
<td>104</td>
<td>2.0</td>
<td>Complies</td>
</tr>
<tr>
<td>Casino</td>
<td>6</td>
<td>101</td>
<td>1.4</td>
<td>Complies</td>
</tr>
<tr>
<td>KEMSA F</td>
<td>6</td>
<td>98</td>
<td>3.1</td>
<td>Complies</td>
</tr>
<tr>
<td>KEMSA C</td>
<td>6</td>
<td>99.4</td>
<td>5.7</td>
<td>Complies</td>
</tr>
<tr>
<td>KEMSA B</td>
<td>6</td>
<td>101</td>
<td>2.3</td>
<td>Complies</td>
</tr>
</tbody>
</table>

NB. No tablet should have <80% dissolution

Table 4. 4 Dissolution of Isoniazid in the Fixed Dose Combination by Facility

<table>
<thead>
<tr>
<th>Facility</th>
<th>N</th>
<th>Mean Dissolution (%)</th>
<th>Relative Standard Deviation (RSD)</th>
<th>Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kisauni HC</td>
<td>6</td>
<td>88.3</td>
<td>1.4</td>
<td>Complies</td>
</tr>
<tr>
<td>Kombeni HC</td>
<td>6</td>
<td>92.8</td>
<td>7.7</td>
<td>Complies</td>
</tr>
<tr>
<td>Diani HC</td>
<td>6</td>
<td>83.7</td>
<td>3.0</td>
<td>Complies</td>
</tr>
<tr>
<td>Rhodes</td>
<td>6</td>
<td>90.8</td>
<td>3.9</td>
<td>Complies</td>
</tr>
<tr>
<td>Casino</td>
<td>6</td>
<td>92.7</td>
<td>4.5</td>
<td>Complies</td>
</tr>
<tr>
<td>KEMSA F</td>
<td>6</td>
<td>94.6</td>
<td>1.9</td>
<td>Complies</td>
</tr>
<tr>
<td>KEMSA C</td>
<td>6</td>
<td>92.9</td>
<td>2.5</td>
<td>Complies</td>
</tr>
<tr>
<td>KEMSA B</td>
<td>6</td>
<td>92.7</td>
<td>1.7</td>
<td>Complies</td>
</tr>
</tbody>
</table>

Table 4. 5 Dissolution of Rifampicin in the Fixed Dose Combination by facility

<table>
<thead>
<tr>
<th>Facility Store</th>
<th>N</th>
<th>Mean Dissolution (%)</th>
<th>Relative Standard Deviation (RSD)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kisauni HC</td>
<td>6</td>
<td>89.6</td>
<td>6.4</td>
<td>Complies</td>
</tr>
<tr>
<td>Kombeni HC</td>
<td>6</td>
<td>96</td>
<td>6.3</td>
<td>Complies</td>
</tr>
<tr>
<td>Diani HC</td>
<td>6</td>
<td>58.8</td>
<td>10</td>
<td>Does not Comply</td>
</tr>
<tr>
<td>Rhodes</td>
<td>6</td>
<td>90</td>
<td>8.1</td>
<td>Complies</td>
</tr>
<tr>
<td>Casino</td>
<td>6</td>
<td>90.9</td>
<td>4.4</td>
<td>Complies</td>
</tr>
<tr>
<td>KEMSA F</td>
<td>6</td>
<td>90.4</td>
<td>3.0</td>
<td>Complies</td>
</tr>
<tr>
<td>KEMSA C</td>
<td>6</td>
<td>80.4*</td>
<td>23.2</td>
<td>Does not Comply</td>
</tr>
<tr>
<td>KEMSA B</td>
<td>6</td>
<td>79.5</td>
<td>3.9</td>
<td>Does not Comply</td>
</tr>
</tbody>
</table>

*One of the tablets had dissolution less than 80%
Table 4. 6 Dissolution of Pyrazinamide in the Fixed Dose Combination by Facility

<table>
<thead>
<tr>
<th>Facility</th>
<th>N</th>
<th>Mean Dissolution (%)</th>
<th>Relative Standard Deviation (RSD)</th>
<th>Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kisauni HC</td>
<td>6</td>
<td>94</td>
<td>2.0</td>
<td>Complies</td>
</tr>
<tr>
<td>Kombeni HC</td>
<td>6</td>
<td>94.1</td>
<td>1.7</td>
<td>Complies</td>
</tr>
<tr>
<td>Diani HC</td>
<td>6</td>
<td>95.9</td>
<td>1.1</td>
<td>Complies</td>
</tr>
<tr>
<td>Rhodes</td>
<td>6</td>
<td>92.8</td>
<td>2.5</td>
<td>Complies</td>
</tr>
<tr>
<td>Casino</td>
<td>6</td>
<td>94.9</td>
<td>2.1</td>
<td>Complies</td>
</tr>
<tr>
<td>KEMSA</td>
<td>6</td>
<td>97.6</td>
<td>1.4</td>
<td>Complies</td>
</tr>
<tr>
<td>KEMSA</td>
<td>6</td>
<td>97.6</td>
<td>7.5</td>
<td>Complies</td>
</tr>
<tr>
<td>KEMSA</td>
<td>6</td>
<td>95.6</td>
<td>1.6</td>
<td>Complies</td>
</tr>
</tbody>
</table>

4.2.4 Assay of active ingredients in FDC Tablets

An assay is an investigative (analytic) procedure in a laboratory measuring the amount of the active ingredients in the four fixed dose anti-tuberculosis drugs. This was done at the NQCL. According to the International Pharmacopeia specifications; assay limit is between 90.0 % and 110.0% of the stated label claim.

Results obtained from the HPLC for the four fixed dose tablets for assay of Ethambutol are given in Table 4.7. Assay for Ethambutol for sampled FDC drugs ranged from 92% for Kombeni health centre to 112% for Kisauni health centre. FDC assay for Ethambutol for drugs from Kisauni Health centre at 112% was outside the higher specification limit.

Table 4.8, indicates the results of Rifampicin assay per facility. It is noted that the assay of Rifampicin was less than the minimum 90% limit for drugs sampled from five facilities and one facility had 90%, two facilities had 98% and 101%.
Table 4.9 above, indicates the results of the assay of Isoniazid per facility. The assay for Isoniazid in the FDC ranged between 91% in Kombeni HC and 101% in Casino. The assay of Isoniazid complied with the specifications in all facilities.

From table 4.10 above, the assay for Pyrazinamide in the FDC for drugs sampled ranged between 90.3% for Kombeni to 110% for Diani. The results indicate that the assay for Pyrazinamide complied with specifications in all the facilities.

Table 4.7 Assay of Ethambutol in the Fixed Dose Combination per Facility

<table>
<thead>
<tr>
<th>Facility</th>
<th>N</th>
<th>Assay (%)</th>
<th>Relative Standard Deviation (RSD)</th>
<th>Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kisauni HC</td>
<td>8</td>
<td>112</td>
<td>0.9</td>
<td>Does not Comply</td>
</tr>
<tr>
<td>Kombeni HC</td>
<td>12</td>
<td>92</td>
<td>1.1</td>
<td>Complies</td>
</tr>
<tr>
<td>Diani HC</td>
<td>12</td>
<td>97</td>
<td>1.2</td>
<td>Complies</td>
</tr>
<tr>
<td>Rhodes</td>
<td>12</td>
<td>101</td>
<td>1.9</td>
<td>Complies</td>
</tr>
<tr>
<td>Casino</td>
<td>12</td>
<td>102</td>
<td>0.6</td>
<td>Complies</td>
</tr>
<tr>
<td>KEMSA F</td>
<td>11</td>
<td>101</td>
<td>1.1</td>
<td>Complies</td>
</tr>
<tr>
<td>KEMSA C</td>
<td>12</td>
<td>101</td>
<td>0.6</td>
<td>Complies</td>
</tr>
<tr>
<td>KEMSA B</td>
<td>12</td>
<td>103</td>
<td>1.7</td>
<td>Complies</td>
</tr>
</tbody>
</table>

Table 4.8 Assay of Rifampicin in Fixed Dose Combination per Facility

<table>
<thead>
<tr>
<th>Facility</th>
<th>N</th>
<th>Assay (%)</th>
<th>Relative Standard Deviation (RSD)</th>
<th>Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kisauni HC</td>
<td>12</td>
<td>101</td>
<td>1.3</td>
<td>Complies</td>
</tr>
<tr>
<td>Kombeni HC</td>
<td>8</td>
<td>90</td>
<td>1.1</td>
<td>Complies</td>
</tr>
<tr>
<td>Diani HC</td>
<td>12</td>
<td>84.9</td>
<td>1.3</td>
<td>Does not Comply</td>
</tr>
<tr>
<td>Rhodes</td>
<td>9</td>
<td>82.7</td>
<td>2.0</td>
<td>Does not Comply</td>
</tr>
<tr>
<td>Casino</td>
<td>11</td>
<td>87.6</td>
<td>2.0</td>
<td>Does not Comply</td>
</tr>
<tr>
<td>KEMSA F</td>
<td>8</td>
<td>88.4</td>
<td>1.4</td>
<td>Does not Comply</td>
</tr>
<tr>
<td>KEMSA C</td>
<td>12</td>
<td>98</td>
<td>1.7</td>
<td>Complies</td>
</tr>
<tr>
<td>KEMSA B</td>
<td>12</td>
<td>85.2</td>
<td>1.8</td>
<td>Does not Comply</td>
</tr>
</tbody>
</table>
Table 4. 9 Assay of Isoniazid in the Fixed Dose Combination per Facility

<table>
<thead>
<tr>
<th>Facility</th>
<th>N</th>
<th>Assay (%)</th>
<th>Relative Standard Deviation (RSD)</th>
<th>Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kisauni HC</td>
<td>10</td>
<td>93.2</td>
<td>1.9</td>
<td>Complies</td>
</tr>
<tr>
<td>Kombeni HC</td>
<td>11</td>
<td>91</td>
<td>1.9</td>
<td>Complies</td>
</tr>
<tr>
<td>Diani HC</td>
<td>10</td>
<td>95.4</td>
<td>1.8</td>
<td>Complies</td>
</tr>
<tr>
<td>Rhodes</td>
<td>12</td>
<td>98.4</td>
<td>1.9</td>
<td>Complies</td>
</tr>
<tr>
<td>Casino</td>
<td>11</td>
<td>101</td>
<td>1.8</td>
<td>Complies</td>
</tr>
<tr>
<td>KEMSA F</td>
<td>10</td>
<td>99.9</td>
<td>1.9</td>
<td>Complies</td>
</tr>
<tr>
<td>KEMSA C</td>
<td>8</td>
<td>98.1</td>
<td>1.8</td>
<td>Complies</td>
</tr>
<tr>
<td>KEMSA B</td>
<td>12</td>
<td>97.3</td>
<td>1.9</td>
<td>Complies</td>
</tr>
</tbody>
</table>

Table 4. 10 Assay of Pyrazinamide in the Fixed Dose Combination per Facility

<table>
<thead>
<tr>
<th>Facility</th>
<th>N</th>
<th>Assay (%)</th>
<th>Relative Standard Deviation (RSD)</th>
<th>Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kisauni HC</td>
<td>12</td>
<td>100</td>
<td>2</td>
<td>Complies</td>
</tr>
<tr>
<td>Kombeni HC</td>
<td>12</td>
<td>90.3</td>
<td>1.6</td>
<td>Complies</td>
</tr>
<tr>
<td>Diani HC</td>
<td>12</td>
<td>110</td>
<td>1.5</td>
<td>Complies</td>
</tr>
<tr>
<td>Rhodes</td>
<td>11</td>
<td>99</td>
<td>1.9</td>
<td>Complies</td>
</tr>
<tr>
<td>Casino</td>
<td>12</td>
<td>98.4</td>
<td>2</td>
<td>Complies</td>
</tr>
<tr>
<td>KEMSA F</td>
<td>11</td>
<td>99.6</td>
<td>1.7</td>
<td>Complies</td>
</tr>
<tr>
<td>KEMSA C</td>
<td>12</td>
<td>103</td>
<td>1.1</td>
<td>Complies</td>
</tr>
<tr>
<td>KEMSA B</td>
<td>12</td>
<td>101</td>
<td>2</td>
<td>Complies</td>
</tr>
</tbody>
</table>

4.2.5 Overall Analysis of compliance of FDC tablets

Drugs from 1(12.5%) facility failed due to friability, 3 (37.5%), due to dissolution of Rifampicin, 1 (12.5%) due to Ethambutol content (assay) and 5(62.5%) due to Rifampicin content (Figure 4.1). Overall, drugs from only 1 facility (Kombeni dispensary in Coast County) of the eight sampled, representing 12.5%, complied with the specifications and even so, the Rifampicin content was on the borderline. The other drugs
from the 8 facilities including KEMSA failed to comply due to various reasons. Thus, 87.5% of the anti TB drugs failed to comply for various reasons (Table 4.11).

Figure 4.1 Compliance of FDC anti-TB drugs in the sampled facilities
Table 4.11 Overall compliance with specifications (weight, friability, dissolution and assay)

<table>
<thead>
<tr>
<th>County</th>
<th>Facility</th>
<th>Manufacturers name</th>
<th>Final Analytical Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mombasa</td>
<td>Kisauni</td>
<td>Svizera Laboratories</td>
<td>Failed for Ethambutol content</td>
</tr>
<tr>
<td>Kilifi</td>
<td>Kombeni</td>
<td>Svizera Laboratories</td>
<td>Complied but assay for Rifampicin was on low borderline</td>
</tr>
<tr>
<td>Kwale</td>
<td>Diani</td>
<td>Macleods Pharmaceuticals</td>
<td>Failed for dissolution and content of Rifampicin and friability</td>
</tr>
<tr>
<td>Nairobi</td>
<td>Rhodes</td>
<td>Svizera Laboratories</td>
<td>Failed for content of Rifampicin</td>
</tr>
<tr>
<td>Nairobi</td>
<td>Casino</td>
<td>Svizera Laboratories</td>
<td>Failed for Content of Rifampicin</td>
</tr>
<tr>
<td>Nairobi</td>
<td>KEMSA F</td>
<td>Svizera Laboratories</td>
<td>Failed for content of Rifampicin</td>
</tr>
<tr>
<td>Nairobi</td>
<td>KEMSA C</td>
<td>Lupin Ltd</td>
<td>Failed for dissolution of Rifampicin</td>
</tr>
<tr>
<td>Nairobi</td>
<td>KEMSA B</td>
<td>Macleods Pharmaceuticals</td>
<td>Failed for dissolution of Rifampicin</td>
</tr>
</tbody>
</table>

4.3 Association of Quality of FDC drugs between Health facilities and KEMSA

Tabulation of data using two-way tables was performed to determine association of drug quality between health facilities and KEMSA. All drugs from both KEMSA and the Health Centers complied with specification with regard to uniformity of weight, dissolution of Ethambutol, Isoniazid and Pyrazinamide as well as with respect to assays for Isoniazid and Pyrazinamide (Table 4.12). For these tests, there was therefore no difference on quality between drugs sampled from KEMSA and the Health Centers.

Results from tests on friability and assays of Ethambutol indicated that one health facility out of five (20%) failed to comply while samples from all KEMSA sites complied. However, this was not a significant difference ($\chi^2=0.69$, $p=0.41$). Drugs from 4 health centers compared to 1 from KEMSA F complied with respect to dissolution of Rifampicin. Further, drugs from 2 of the KEMSA sites failed to comply with Rifampicin.
dissolution compared to 1 from health centers. Thus there was better compliance of drugs from the Health Centers on dissolution of Rifampicin than for KEMSA drugs. However, the compliance was not significantly different ($\chi^2 = 1.74, p=0.19$).

Drugs from 1 KEMSA C site complied with assay of Rifampicin compared to 2 from health facilities (Kisauni and Kombeni). Further, drugs from 3 health centers (Diani, Rhodes, Casino) compared to 2 from KEMSA (F and B) failed to comply. There was however no significant difference between KEMSA and health facility drugs with regard to Rifampicin assay ($\chi^2 = 0.04, p=0.85$).

Overall, drugs from one health facility (Kombeni) complied with all specifications but assay results for Rifampicin were on the borderline while none from KEMSA complied. Drugs from all KEMSA sites (100%) failed to comply with specifications compared to four out of the five (80%) of health Centers. However, this was not a significant difference ($\chi^2 = 0.69, p=0.41$).
Table 4.12 Association of Quality of FDC drugs between Health facilities and KEMSA

<table>
<thead>
<tr>
<th>Test</th>
<th>Facility</th>
<th>Number Complied</th>
<th>Number did not comply</th>
<th>Chi Squared</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformity of weight</td>
<td>Health Centre</td>
<td>5</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>KEMSA</td>
<td>3</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Friability</td>
<td>Health Centre</td>
<td>4</td>
<td>1</td>
<td>0.69</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>KEMSA</td>
<td>3</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dissolution of Ethambutol</td>
<td>Health Centre</td>
<td>5</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>KEMSA</td>
<td>3</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dissolution of Rifampicin</td>
<td>Health Centre</td>
<td>4</td>
<td>1</td>
<td>1.74</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>KEMSA</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dissolution of Isoniazid</td>
<td>Health Centre</td>
<td>5</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>KEMSA</td>
<td>3</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dissolution of Pyrazinamide</td>
<td>Health Centre</td>
<td>5</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>KEMSA</td>
<td>3</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assay of Rifampicin</td>
<td>Health Centre</td>
<td>2</td>
<td>3</td>
<td>0.04</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>KEMSA</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assay of Ethambutol</td>
<td>Health Centre</td>
<td>4</td>
<td>1</td>
<td>0.69</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>KEMSA</td>
<td>3</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assay of Isoniazid</td>
<td>Health Centre</td>
<td>5</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>KEMSA</td>
<td>3</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assay of Pyrazinamide</td>
<td>Health Centre</td>
<td>5</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>KEMSA</td>
<td>3</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Results</td>
<td>Health Centre</td>
<td>1</td>
<td>4</td>
<td>0.69</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>KEMSA</td>
<td>0</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fisher exact values used since cells contained less than 5
### 4.4 Association of Quality of Fixed Dose Combination drugs between Coast and Nairobi facilities

Drugs from all coast and Nairobi facilities complied with specifications for uniformity of weight, dissolution of Ethambutol, Isoniazid and Pyrazinamide and assay of Isoniazid. There was no observed significant difference in compliance between Coast and Nairobi facilities with respect to friability ($\chi^2=1.90$, $P=0.17$), dissolution of Rifampicin ($\chi^2=0.04$, $P=0.85$), Ethambutol assay ($\chi^2=1.90$, $P=0.17$) and Rifampicin assay ($\chi^2=1.74$, $P=0.19$) (Table 4.13)

**Table 4.13 Association of Quality of Fixed Dose Combination drugs between Coast and Nairobi Facilities**

<table>
<thead>
<tr>
<th>Test</th>
<th>Regions</th>
<th>Complied N (%)</th>
<th>Did not comply N (%)</th>
<th>Chi Squared</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformity of weight</td>
<td>Coast</td>
<td>3(37.5)</td>
<td>0(0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nairobi</td>
<td>5(62.5)</td>
<td>0(0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Friability</td>
<td>Coast</td>
<td>2(28.6)</td>
<td>1(100)</td>
<td>1.9</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>Nairobi</td>
<td>5(71.4)</td>
<td>0(0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dissolution of Ethambutol</td>
<td>Coast</td>
<td>3(37.5)</td>
<td>0(0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nairobi</td>
<td>5(62.5)</td>
<td>0(0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dissolution of Rifampicin</td>
<td>Coast</td>
<td>2(40.0)</td>
<td>1(33.3)</td>
<td>0.04</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>Nairobi</td>
<td>3(60.0)</td>
<td>2(66.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dissolution of Isoniazid</td>
<td>Coast</td>
<td>3(37.5)</td>
<td>0(0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nairobi</td>
<td>5(62.5)</td>
<td>0(0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dissolution of Pyrazinamide</td>
<td>Coast</td>
<td>3(37.5)</td>
<td>0(0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nairobi</td>
<td>5(62.5)</td>
<td>0(0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assay of Rifampicin</td>
<td>Coast</td>
<td>2(66.7)</td>
<td>1(20.0)</td>
<td>1.74</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>Nairobi</td>
<td>1(33.3)</td>
<td>4(80.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assay of Ethambutol</td>
<td>Coast</td>
<td>2(28.6)</td>
<td>1(100)</td>
<td>1.9</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>Nairobi</td>
<td>5(71.4)</td>
<td>0(0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assay of Isoniazid</td>
<td>Coast</td>
<td>3(37.5)</td>
<td>0(0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nairobi</td>
<td>5(62.5)</td>
<td>0(0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assay of Pyrazinamide</td>
<td>Coast</td>
<td>3(37.5)</td>
<td>0(0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nairobi</td>
<td>5(62.5)</td>
<td>0(0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Results</td>
<td>Coast</td>
<td>1(100)</td>
<td>2(28.6)</td>
<td>1.9</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>Nairobi</td>
<td>0(0)</td>
<td>5(71.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.5 Storage conditions practiced by health facilities for the Fixed Dose Combination anti-tuberculosis drugs.

All the drugs were packed in aluminium strip packs. The storage space was adequate in seven of the eight the facilities. All the stores were well ventilated; some using fans while majority were using window ventilation. Seven facilities (87.5%) had shelves but 1 (12.5%) was not shelved. The four fixed dose anti-TB drugs were placed on the floor. Among the facilities with shelves, 5 (71.4%), pallets used were at least 10 cm off the floor while 2(18.6%) were less than 10 cm off the floor. Temperature and humidity was not monitored in any of the facilities although in one facility there was temperature control cards and thermometer which were not used. The storage conditions were in compliance with the labeling requirements in 6(75%) of the facilities. It was also found out that there were anti-TB drugs with broken seals, damaged packs or expired drugs in 2(25%) of the facilities. Motor vehicles were the main mode of transportation from KEMSA, together with motorbikes used to ferry drugs from the District Hospitals to the Health Centers. In all the assessed facilities, drug packages were inspected for damages or expiry on receipt. The ‘First-in-first out’ (FIFO) procedure was practiced in all except one facility. Table 4.14 shows the storage conditions practiced for the FDCs anti-tuberculosis drugs in both KEMSA and Health Center levels.
Table 4. 14: Storage conditions practiced for the Fixed Dose Combination anti-tuberculosis drugs

<table>
<thead>
<tr>
<th>Factor</th>
<th>Response</th>
<th>KEMSA Facilities (%)</th>
<th>Health Centers Facilities (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of packaging</td>
<td>Strip pack</td>
<td>3(100)</td>
<td>5(100)</td>
<td>8(100)</td>
</tr>
<tr>
<td></td>
<td>Loosely packed</td>
<td>0(0)</td>
<td>0(0)</td>
<td>0(0)</td>
</tr>
<tr>
<td></td>
<td>Tightly closed container protected from light</td>
<td>0(0)</td>
<td>0(0)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Storage space adequate</td>
<td>Yes</td>
<td>3(100)</td>
<td>4(80)</td>
<td>7(87.5)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0(0)</td>
<td>1(20)</td>
<td>1(12.5)</td>
</tr>
<tr>
<td>Ventilated</td>
<td>Yes</td>
<td>3(100)</td>
<td>4(80)</td>
<td>7(87.5)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0(0)</td>
<td>1(20)</td>
<td>1(12.5)</td>
</tr>
<tr>
<td>Shelving</td>
<td>Yes</td>
<td>3(100)</td>
<td>4(80)</td>
<td>7(87.5)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0(0)</td>
<td>1(20)</td>
<td>1(12.5)</td>
</tr>
<tr>
<td>Pallets used at least 10cm off floor</td>
<td>Yes</td>
<td>3(100)</td>
<td>3(60)</td>
<td>6(75.0)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0(0)</td>
<td>2(40)</td>
<td>2(25.0)</td>
</tr>
<tr>
<td>Temperature and humidity monitored</td>
<td>Yes</td>
<td>0(0)</td>
<td>0(0)</td>
<td>0(0)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>3(100)</td>
<td>5(100)</td>
<td>8(100)</td>
</tr>
<tr>
<td>Storage conditions comply with labeling requirements</td>
<td>Yes</td>
<td>3(100)</td>
<td>3(60)</td>
<td>6(75.0)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0(0)</td>
<td>2(40)</td>
<td>2(25.0)</td>
</tr>
<tr>
<td>Drugs stored on floor</td>
<td>Yes</td>
<td>0(0)</td>
<td>1(20)</td>
<td>1(12.5)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>3(100)</td>
<td>4(80)</td>
<td>7(87.5)</td>
</tr>
<tr>
<td>Drugs with broken seals, damaged packs or expired</td>
<td>Yes</td>
<td>0(0)</td>
<td>2(40)</td>
<td>2(25.0)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>3(100)</td>
<td>3(60)</td>
<td>6(75.0)</td>
</tr>
<tr>
<td>Inspect packages for damaged or expired drugs on receipt</td>
<td>Yes</td>
<td>3(100)</td>
<td>5(100)</td>
<td>8(100)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0(0)</td>
<td>0(0)</td>
<td>0(0)</td>
</tr>
<tr>
<td>First in first out practiced</td>
<td>Yes</td>
<td>3(100)</td>
<td>5(100)</td>
<td>8(100)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0(0)</td>
<td>0(0)</td>
<td>0(0)</td>
</tr>
<tr>
<td>First Expiry first out practiced</td>
<td>Yes</td>
<td>3(100)</td>
<td>4(80)</td>
<td>7(87.5)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0(0)</td>
<td>1(20)</td>
<td>1(12.5)</td>
</tr>
<tr>
<td>Temperature control cards/thermometer present</td>
<td>Yes</td>
<td>0(0)</td>
<td>0(0)</td>
<td>8(100)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>3(100)</td>
<td>5(100)</td>
<td>8(100)</td>
</tr>
</tbody>
</table>
CHAPTER 5: DISCUSSION

5.1 Assay of the active ingredients in FDC anti-TB drugs

This study presents important findings on the assessment of the four fixed dose anti-TB drugs in terms of assay, uniformity of weight, friability and dissolution. These four specifications must be complied with as per the USP (2006) for the FDC drug to be certified as quality drug for use in TB treatment. The main goal in the Kenya National Pharmaceutical Policy of (2008) is to ensure the provision to all Kenyans of efficient, effective pharmaceutical services that are sustainable, equitable, accessible and affordable with safe, efficacious and quality essential medicines which are appropriately used. One of the objectives of the TB control according to the (NLTP, 2005) Guidelines is to prevent drug resistance, of course by provision of quality drugs. Drugs from all KEMSA sites and from four of the five of health Centers failed to comply with specifications.

Available data from a study done by Kenyon et al. (1999) in Gaborone, Botswana indicated that 31% of the FDCs that were analyzed had low content of Rifampicin, the most important bactericidal TB drug in the FDC. It was explained that the source of poor drug quality could have arisen due to poor manufacturing practices, counterfeiting or inappropriate drug storage in excessive heat, moisture or light. This study has shown that assay of Rifampicin was below the 90% low limits in five health facilities including KEMSA where drugs are received from manufacturers. The low content of Rifampicin may be explained by the fact that FDCs are associated with loss of Rifampicin bioavailability and instability of the drugs in the combination. (Saranjit Singh et al., 2006). Explanation given for loss of Rifampicin bioavailability is due to the Rifampicin and
Isoniazid reaction under empty stomach conditions whereby significant loss of Rifampicin occurs before absorption. Rifampicin is first hydrolyzed to form 3-formylrifamycin which further reacts with Isoniazid to form isonicotinyl hydrazone (HYD). This then converts back to Isoniazid and 3 formylrifamycin resulting in the recovery of Isoniazid and eventually causing the loss of Rifampicin (Saranjit et al., 2006).

Available data from (WHO, 2000) indicates treatment of TB with poor quality drugs will not only result in treatment failures but can lead to the development of drug resistance. This will have a deleterious effect on the health of the wider population. Ensuring the quality, safety and efficacy of all anti-TB drugs, including FDCs, used in a NLTP, is therefore of utmost importance in combating the disease. Safety, efficacy and quality are built into a product at the time of its design and production. This means that quality; safety and efficacy of FDC drugs are determined by the manufacturing process that is, compliance of the manufacturer with the requirements of good manufacturing practices (GMP) and pharmacopoeial specifications. However, a FDC product which has been produced in full compliance with GMP requirements and has passed all laboratory tests may lose its quality and eventually become ineffective if the packaging, storage and transportation conditions are substandard. This study observed that the storage conditions in all health facilities were satisfactory. Consequently, in order to ensure that FDC products are safe, effective and of good quality, national NLTP programme must establish a QA system addressing the following issues:
i. Production of FDC products in accordance with GMP requirements

ii. Storage, transport and distribution of FDC products under appropriate conditions

(that is conditions stated by the manufacturer and appearing on the labels of the products)

Explanation also given by Saranjit et al. (2006) is that when Ethambutol absorbs moisture, acidic hydrolytic environment is formed thus accelerates the reaction between Rifampicin and Isoniazid which later converts back to full recovery of Isoniazid and loss of Rifampicin.

5.2. Dissolution of FDC Tablets

Results of this study showed that Rifampicin again has a problem with dissolution in three out of eight facilities. The most important drug in the combination Rifampicin failed to meet the dissolution specifications. Dissolution is a measure of the ability of the ingested drug to be dissolved and absorbed into the blood system. Dissolution of Rifampicin is decreased when it is combined with other drugs in the FDC.

5.3 Friability

This is a parameter that indicates that a drug can withstand transportation pressures without breaking down. Excipients added during manufacture if not in proper proportions as per the Pharmacopoeial specifications, the tablet may not disintegrate. If the tablet like in this study fails to comply with the specifications, it means that the tablets were mishandled during transportation.

From this study, it was noted that the mode of transport of the anti-TB drugs from Msambweni hospital to Diani health center was via a motorbike. This may have affected
the tablets being transported and in this case, friability may have been affected as it failed to comply with the specifications for friability.

5.4 Storage Conditions

According to a study done by Laserson et al. (2001) adherence to guidelines to proper storage of drugs protected from heat, humidity and sunlight is important in maintaining quality of these drugs. Anti-TB drugs and if not properly stored will affect TB treatment outcomes. In this study storage conditions in health facilities and KEMSA were fairly complied based on a post market surveillance of first line anti-Tuberculosis medicines conducted in Kenya in 2010 indicated that 78% of the sites had appropriate storage conditions. This available data compares well with the findings of this study.

5.5 Compliance to specifications of drug samples in KEMSA and Health Centers

Drugs sampled from KEMSA and Health facilities indicated that overall, drugs from all KEMSA sites failed to comply with specifications compared to four out of the five of health facilities. This indicates that the problem of poor quality is most likely due to poor manufacturing practices by the manufacturer. It should be noted that KEMSA is the first entry point of drugs from the manufacturers before they are distributed to district stores then to the health facilities. Good Manufacturing Practices (GMP) is that part of QA which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. WHO has provided a guideline for GMP. In principle these are production operations which are clearly defined procedures in manufacturing of a pharmaceutical product, with the objective of obtaining products of requisite quality and that proper quality control is put in place.
5.5.1 Control of starting materials

Rifampicin and Isoniazid

In a WHO meeting held in Geneva in 1999 on fixed dose combination tablets, for the treatment of tuberculosis, it was recommended that quality raw materials must be used in the manufacture of fixed drug combination. There should be a rigid regulation of the sources of and crystalline form of Rifampicin. Rifampicin shows polymorphism 1 and 2. The USP specifies that crystalline form 2 be used in all Rifampicin preparations. Rifampicin as an active pharmaceutical ingredient is unstable and can undergo hydrolysis and oxidation. Therefore the manufacture of the fixed dose combination and the primary packaging materials of Active Pharmaceutical Product (API) require attention to protect Rifampicin as well as from light because Rifampicin is light sensitive, by using protective film coating or protective packaging. Isoniazid as an API can react with Rifampicin to form a hydrazone (Saranjit et al. 2006). Therefore contact between these two APIs during manufacture should be reduced to a minimum.

Ethambutol hydrochloride

Ethambutol hydrochloride is hygroscopic (Singh et al. 2002). This property should be taken into account during product development of FDCs containing this API, including the selection of the primary packaging material for the API and Finished Pharmaceutical (FPP). The presence of Ethambutol hydrochloride in an Isoniazid/Rifampicin FDC can create further problems due to its hygroscopicity (water serves as solvent for degradation) and acidic nature. These complex API-API incompatibility problems should be carefully considered during formulation development and manufacturing process development (Saranjit et al., 2006). Storage conditions practised by health facilities indicates that
packaging of all fixed dose combinations anti-TB drugs was amber coloured strip packing. This sort of packaging protects the drug from absorbing moisture, light and excessive heat. However this study findings and the study by (Saranjit et al. 2006) show that the packaging did not adequately prevent absorption of water by Ethambutol (Kenyon et al., 1999) thus creating a liquid environment good for degradation of the drug combination and lowering Rifampicin assay and dissolution. The labelling that the drug should be stored below 30°C, protected from light.

5.5.2 Post market Surveillance (PMS)

Available data from Tomans/WHO, 2004, CDC 2003, Thoithi et al. 2002, and MOH/CDC, 2010 on post market surveillance indicate that fixed dose combination drugs in the market fail to comply with the specifications and therefore are substandard. This study has confirmed that there are substandard fixed dose combinations in the market especially those with low content of Rifampicin and low dissolution profile. Although there may be proven bioavailability during the approval or tender process, there is often no systematic mechanism to ensure that all subsequent batches of FDCs also have adequate bioavailability. The regulatory structures required to adequately monitor GMP and ensure bioavailability standards for FDCs (either imported or local) should be strengthened. The Pharmacy and Poisons Board in its regular Pharmacovigilance newsletter encourages reporting of poor quality medicines in the market. The board has taken regulatory actions to enhance patient safety and over 1400 suspected adverse drug reactions and poor quality reports received in 2009 (PPB, 2011)
CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

This study sought to assess the quality of the four fixed dose combination of anti-TB drugs used in the first line treatment of TB patients. The active content (assay), uniformity of weight, friability, and dissolution of the FDCs anti-TB drugs sampled from Nairobi and Coast Counties for compliance with the required quality specifications in the International Pharmacopoeia. The study also assessed the storage conditions practiced by health facilities for FDCs and KEMSA and compared the quality of sampled FDCs from health facilities with those from KEMSA. These drugs were bought, stored and supplied by KEMSA to all health facilities. The study was guided by the following hypothesis:

The quality of four fixed dose combination anti-TB drug supplied by NLTP meets the International Pharmacopoeia standards.

The sampled anti-TB drugs originated from three different manufacturers, namely Svizera Labs, Lupin Ltd and Macleods pharmaceuticals. Drugs from Svizera Labs India were distributed in 5(62.5%) of the facilities while those from Macleods and Lupin Ltd were distributed in 2(25%) and 1(12.5%) facilities respectively. Majority of sampled tablets 896 (65.9%) were from Svizera Laboratory India, 352(25.9%) from Macleods Pharmaceuticals and 112(8.2%). The type of packaging used in all the drugs was aluminium foil strip packs of either 10 or 28 tablets each and were within the expiry date. All samples were well labeled with batch numbers, manufacturing and expiry dates. Storage condition was indicated as store in a cool, dry place below 25°C, protected from light.
Drugs from 1(12.5%) facility failed due to friability, 3(37.5%) due to dissolution of Rifampicin, 1(12.5%) due to Ethambutol content (assay) and 5(62.5%) due to Rifampicin content. Overall, drugs from only one facility (Kombeni dispensary in Coast province) of the eight sampled, representing 12.5%, complied with the specifications and even so, the Rifampicin content was on the borderline. These drugs were manufactured by Svizera Labs, India. All the other drugs from the 8 facilities including KEMSA failed to comply due to various reasons. Thus, 87.5% of the anti TB drugs failed to comply for various reasons.

From the results of this study it is concluded that:

i. Overall, drugs from majority of the facilities, 7 out of 8, failed to comply with specifications (87.5%)

ii. Rifampicin content and dissolution failed to comply with the specifications in most of the facilities

iii. There was no observed significant difference in compliance between Coast and Nairobi facilities with respect to friability, dissolution of Rifampicin, Ethambutol assay and Rifampicin assay

iv. Storage conditions for the TB drugs were generally satisfactory in all KEMSA sampled points, but in health facilities storage conditions were inadequate.

v. Temperature and Humidity was not monitored in any of the facilities although in one site in KEMSA, temperature control card and thermometer were present but not used
6.2 Recommendations

i. Batch to batch analysis of all anti-TB drugs to be undertaken by KEMSA before receipt from manufacturers.

ii. Withdrawal of substandard drugs from the market by the Regulatory Authority.

iii. The Pharmacy and Poisons Board should continuously monitor the quality of anti-TB drugs in the market.

iv. Enlarge study to cover all the counties in Kenya.

6.3 Suggestions for further study

i. Rifampicin in the combination with other drugs presents bioavailability problems in the stomach where environment is acidic. Further study needs to be done to investigate limit absorption of the fixed dose combination in the acidic environment and documentation done in Kenya.

ii. A study needs to be done to find out if there is a relationship between multi-drug resistance to TB and the quality of the Fixed Dose Combination drugs available in Kenya.
REFERENCES


Director General of Health Services, India, 2011 Guidelines for the storage of anti-TB drugs, New Delhi

Division of Leprosy Tuberculosis Lung Disease, annual report (DLTLD, 2009)

International Council of Nurses (ICN, 2005) Targetting Counterfeits and Substandard Medicines

IUATLD, 2001, A guide for the procurement of anti-TB Drugs Paris, France


World Health Organization (WHO, 2002). Operational guide for National Tuberculosis Control Programmes on the Introduction and use of Fixed-Dose Combination Drugs


APPENDIX 1a: Study area (Nairobi County)
APPENDIX 1b: Study area (Coast Counties)
APPENDIX 2: DATA COLLECTION TOOLS

Assessment of quality of four fixed dose combination anti-TB drugs in Nairobi.
Mombasa, Kwale and Kilifi Counties.

a) Observation Check List

1. Name of County---------------------------------------------

2. Name of district---------------------------------------------

3. Name of Health facility-------------------------------------

4. Name of Data Collector--------------------------------------

5. Drug particulars

   a) Name of the drug-------------------------------------------

   b) Dosage form-----------------------------------------------

   c) Batch no.-----------------------------------------------

   d) Manufacturing date----------------------------------------

   e) Expiry date-----------------------------------------------

   f) Name of Manufacturer-------------------------------------

   g) Country of origin------------------------------------------

   h) Type of Packaging (tick as appropriate)

      i) Strip pack---------------------------------

      ii) Loosely packed-------------------

      iii) Tightly closed container protected from light-------

6. Storage conditions: make observations/describe

   a) Storage space---------------------------------------------

   b) Ventilated-----------------------------------------------
c) Shelving

d) Pallets used (at least 10cm) off the floor

e) Temperature and humidity monitored

f) Storage conditions in compliance with the labeling requirements

h) Are there any four fixed dose combination anti-TB drugs stored on the floor?  

i) Are there any four fixed dose combination anti-TB drugs with broken seals, damaged packs or expired?  

j) Mode of transportation from KEMSA

k) Date dispatched from KEMSA

k) Date received at facility

k) Storage duration

b) Interview schedule

a) Do you inspect packages for damaged or expired drugs on receipt? Yes/No

b) Is First in/First out policy (FIFO) used? Yes/No

c) Is First Expiry First out (FEFO) Policy used? Yes/No

d) Do you use thermometer and temperature control cards? Yes/No

c) Laboratory Request Form with the following details:

1. Name of Product
2. Type of the Product
3. Tests required
   a) Uniformity of weight
   b) Friability
   c) Assay
d) Dissolution

4. Name and signature of person requesting for analysis------------------------

d) Analytical Laboratory Report for the drug.

Name of Product ---------------------------------------------------------------

Batch Number------------------------------------------------------------------

Name of health facility--------------------------------------------------------

Name of Manufacturer----------------------------------------------------------

Active Ingredient (Assay) -----------------------------------------------------

Labeled Weight/dosage form----------------------------------------------------

Chemical Content (%label Claim) -----------------------------------------------

Dissolution Test (Q %) --------------------------------------------------------

Friability---------------------------------------------------------------------

Uniformity of Weight-----------------------------------------------------------
APPENDIX 3: AUTHORITY TO CONDUCT RESEARCH

MINISTRY OF SCIENCE AND TECHNOLOGY

Telegram: SCIENCE TECH', Nairobi
Telephone: Nairobi 318581
Email: ps@science andtechnology.go.ke
When replying please quote

JOGOO HOUSE "B"
HARAMBEE AVENUE
P.O. BOX 9583-00200
NAIROBI

16th Nov. 2007

Dr. Bibiana Kanduka Njue
P.O. Box 67350 - 00200
NAIROBI.

Dear Madam,

RE: RESEARCH AUTHORIZATION

Following your application for authority to conduct research on Quality Assessment of four fixed dose combination Anti-Tuberculous drugs in Nairobi and Coast Provinces, this is to inform you that you have been authorized to conduct research in Coast and Nairobi Provinces for a period ending 31st Jan 08.

You have been advised to report to the Provincial Commissioners and the Provincial Medical Officers of Health in Nairobi and Coast Provinces before commencing your study. On completion, you are expected to submit two copies of your research report to this office.

Yours faithfully,

M. O. Ondieki
For Permanent Secretary

Cc. The Provincial Commissioner
    Nairobi.

Cc. The Provincial Commissioner
    Coast Province.

Cc. Provincial Medical Officer
    Coast Province.

Cc. Provincial Medical Officer
    Nairobi Province.
# APPENDIX 4: CERTIFICATES OF ANALYSIS

![Certificate Image]

**PRODUCT:** A-KurIT - 4 TABLETS  
**DATE RECEIVED:** 30.12.2007  
**BATCH NO.:** 80215  
**MFG. DATE:** Jun. 2006  
**EXP. DATE:** May. 2008  
**CLIENT REF NO.:** M1  
**MANUFACTURER:** LUPIN LTD.  
**ADDRESS:** A - 28/I, M.I.D.C., Chikhali, Aurangabad – 431 210, INDIA  
**CLIENT:** Dr. Nipa, c/o Pharmacy and Poisons Board, P.O. Box 27653, NAIROBI.  
**REF NO.:** NDQD200712484

## CERTIFICATE OF ANALYSIS

**TEST(S) REQUESTED:** Dissolution, Friability and Assay.  
**RESULTS**

<table>
<thead>
<tr>
<th>TEST</th>
<th>METHOD</th>
<th>COMPENDIA</th>
<th>SPECIFICATION</th>
<th>DETERMINED</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformity of Weight</td>
<td>Weight</td>
<td>B.P. 2007 Vol IV App XIV G</td>
<td>≤ 2 tablets deviate by more than 5% from mean</td>
<td>None Deviates</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Friability</td>
<td>Friability &amp; Weight</td>
<td>B.P. 2007 Vol IV App XVIE G</td>
<td>≤ 1%</td>
<td>0.01%</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Dissolution</td>
<td>HPLC</td>
<td>USP 29 NF 24 Page 1922</td>
<td>No tablet less than 80%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assay</td>
<td>HPLC</td>
<td>USP 29 NF 24 Page 1922</td>
<td>90.0 - 100.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CONCLUSION:** The product fails to comply with the specification for content of Ethambutol.

**ANALYST:** MR. N. BERGEN  
**DATE:** 11/01/2008  
**ANALYST:** DR. S. MUTERU  
**DATE:** 11/01/2008  
**ANALYST:** DR. G. WANG'ANGA  
**DATE:** 11/01/2008  
**DIRECTOR:** DR. H. K. CHEPKWONY  
**DATE:** 11/01/2008
# National Quality Control Laboratory

**RO. Box 29726, 00202 Nairobi**
**Telephone: 2726963**
**Fax: 2718073**

**CERTIFICATE OF ANALYSIS**

**CERTIFICATE No: CAN/2008/007**

## PRODUCT:
RIFAMPICIN / ISONIAZID / PYRAZINAMIDE / ETHAMBUTOL HYDROCHLORIDE TABLETS

## LABEL CLAIM:

## PRESENTATION:
Brown coloured film coated, caplet shaped, biconvex face tablets single scored on one face and plain on the other. Packed in blister strips in a box carrying 8 strips of 28 tablets each.

## MANUFACTURER:
SVIZERA LABS.

## ADDRESS:
Mumbai, INDIA

## CLIENT:
Dr. NJie, c/o Pharmacy and Poisons Board, P.O. Box 27665, NAIROBI.

## TEST(S) REQUESTED:
Dissolution Friability and Assay.

## RESULTS

<table>
<thead>
<tr>
<th>TEST</th>
<th>METHOD</th>
<th>COMPENDIA</th>
<th>SPECIFICATION</th>
<th>DETERMINED</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformity of Weight Frability &amp; Weight</td>
<td>Weight</td>
<td>B.P. 2007 Vol IV App XE G</td>
<td>≤ 2 tablets deviate by more than 5% from mean</td>
<td>None Deviates</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Frability &amp; Weight</td>
<td>Friability &amp; Weight</td>
<td>B.P. 2007 Vol IV App XVII G</td>
<td>≤ 1%</td>
<td>0.01%</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Dissolution</td>
<td>HPLC</td>
<td>USP 29 NF 24 Page 1922</td>
<td>No tablet less than 80%</td>
<td>Ethambutol 97.1% (n=6; RSD=1.6%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rifampicin 96.6% (n=6; RSD=6.3%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Isoniazid 92.8% (n=6; RSD=7.7%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pyrazinamide 94.1% (n=6; RSD=1.7%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td>Assay</td>
<td>HPLC</td>
<td>USP 29 NF 24 Page 1922</td>
<td>90.0 - 110.0%</td>
<td>Ethambutol 92.4% (n=12; RSD=1.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rifampicin 90.0% (n=8; RSD=1.1%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Isoniazid 91.0% (n=11; RSD=1.9%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pyrazinamide 90.3% (n=12; RSD=1.8%)</td>
<td>COMPLIES</td>
</tr>
</tbody>
</table>

## CONCLUSION:
The product complies with the specifications for the tests performed. However, the assay results of Rifampicin was found to be bordering on the lower acceptable limit.

**ANALYST:** MR. N. BERGEN  
**DATE:** 11/01/2008

**ANALYST:** DR. S. MUTEBI  
**DATE:** 11/01/2008

**ANALYST:** DR. G. WANG ANGA  
**DATE:** 11/01/2008

**DIRECTOR:** DR. H. K. CHEPKONNY  
**DATE:** 11/01/2008
# NATIONAL QUALITY CONTROL LABORATORY

**P.O. Box 29726, 00202 Nairobi • Telephone: 2726963 • Fax: 2718073**

## CERTIFICATE OF ANALYSIS

**CERTIFICATE No: CAN/2008/005**

<table>
<thead>
<tr>
<th>PRODUCT:</th>
<th>REF. NO:</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIFAMPICIN / ISONIAZID / PYRINAZIMIDE / ETHAMBUTOL HYDROCHLORIDE TABLETS</td>
<td>NDQD2009/11475</td>
</tr>
</tbody>
</table>

**DATE RECEIVED:** 11.01.2007

**BATCH NO.:** S1793

**MG. DATE:** Jan 2011

**EXP. DATE:** Dec 2011

**CLIENT REF. NO.:** NA

**ADDRESS:** Mumbai, INDIA

**MANUFACTURER:** SVITZA LABS.

**LABEL CLAIM:** Each film coated tablet contain 5 mg Rifampicin U.S.P., 75 mg Isoniazid U.S.P., and 333 mg Pyrazinamide U.S.P. 50 mg Ethambutol Hydrochloride U.S.P. 275 mg.

**PRESENTATION:** Brown coloured film coated, caplet shaped, biconvex faced tablets single scored on one face and plain on the other.

**TEST(S) REQUESTED:** Dissolution, Friability and Assay.

## RESULTS

<table>
<thead>
<tr>
<th>TEST</th>
<th>METHOD</th>
<th>COMPENDIA</th>
<th>SPECIFICATION</th>
<th>DETERMINED</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformity of Weight</td>
<td>Weight</td>
<td>B.P. 2005 Vol IV App XII G</td>
<td>&lt;= 2 tablets deviate by more than 5% from mean</td>
<td>None Deviates</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Friability and Weight</td>
<td>Friability &amp; Weight</td>
<td>B.P. 2005 Vol IV App XVII G</td>
<td>&lt;= 1%</td>
<td>0.00%</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Dissolution</td>
<td>HPLC</td>
<td>USP 29 NF 24 Page 1922</td>
<td>No tablet less than 100%</td>
<td>Ethambutol: 104% (n=5, RSD=2.6%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rifampicin: 90.0% (n=5, RSD=8.1%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Isoniazid: 90.8% (n=5, RSD=8.5%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pyrazinamide: 92.8% (n=5, RSD=2.5%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Assay</td>
<td>HPLC</td>
<td>USP 29 NF 24 Page 1922</td>
<td>90.0 - 110.0%</td>
<td>Ethambutol: 101% (n=12, RSD=1.9%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rifampicin: 82.7% (n=5, RSD=2.0%)</td>
<td>DOES NOT COMPLY</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Isoniazid: 98.4% (n=12, RSD=1.9%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pyrazinamide: 99.0% (n=1, RSD=1.9%)</td>
<td>COMPLIES</td>
</tr>
</tbody>
</table>

## CONCLUSION:
The product fails to comply with the specifications for content of Rifampicin.

**ANALYST:** MR. N. BERGEN

**ANALYST:** DR. S. MUTERU

**ANALYST:** DR. G. WANGANGA

**DIRECTOR:** DR. H.K. CHEPKWONY

**DATE:** 11/01/2008
# Certificate of Analysis

**Product:** Rifampicin / Isoniazid / Pyrazinamide / Ethambutol hydrochloride tablets

**Label Claim:** Each film coated tablet contains: Rifampicin U.S.P. 150 mg, Isoniazid U.S.P. 75 mg, Pyrazinamide U.S.P. 450 mg, Ethambutol Hydrochloride U.S.P. 275 mg.

**Presentation:** Brown coloured film coated, caplet shaped, biconvex faced tablets single scored on one face and plain on the other.

**Note:** Samples not submitted in manufacturer's secondary packaging.

**Manufacturer:** SVIZERA LABS.

**Address:** Mumbai, India

**Client:** Dr. Njie, c/o Pharmacy and Poisons Board, P.O. Box 27063, NAIROBI

**Test(s) Requested:** Dissolution, Friability and Assay.

## Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Method</th>
<th>Compendia</th>
<th>Specification</th>
<th>Determined</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformity of Weight</td>
<td>Weight</td>
<td>B.P. 2007 Vol IV App XLI G</td>
<td>≤ 2 tablets deviate by more than 5% from mean</td>
<td>None Deviates</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Friability Weight</td>
<td>Friability &amp; Weight</td>
<td>B.P. 2007 Vol IV App XVII G</td>
<td>≤ 1%</td>
<td>0.004%</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Dissolution</td>
<td>HPLC</td>
<td>USP 29 NF 24 Page 1922</td>
<td>No tablet less than 80%</td>
<td>Ethambutol: 101% (n=6, RSD=1.4%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Isoniazid: 92.7% (n=6, RSD=4.5%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rifampicin: 90.9% (n=6, RSD=4.4%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pyrazinamide: 94.9% (n=6, RSD=2.1%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Assay</td>
<td>HPLC</td>
<td>USP 29 NF 24 Page 1922</td>
<td>90.0% - 110.0%</td>
<td>Ethambutol: 102% (n=12, RSD=6.6%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rifampicin: 87.6% (n=11, RSD=2.0%)</td>
<td>DOES NOT COMPLY</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Isoniazid: 101% (n=11, RSD=5.8%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pyrazinamide: 98.4% (n=12, RSD=2.0%)</td>
<td>COMPLIES</td>
</tr>
</tbody>
</table>

## Conclusion

The product fails to comply with the specifications for content of Isoniazid.

**Analyst:** Mr. N. Birgin
**Analyst:** Dr. S. Mutuku
**Analyst:** Dr. G. Wang'ang'a
**Director:** Dr. H. K. Chepkwon

**Date:** 11/01/2008
# National Quality Control Laboratory

**CERTIFICATE OF ANALYSIS**

**PRODUCT:** Forecox - Trac Tablets

**REF. NO.:** NDQD2007114/6


**PRESENTATION:** Peach coloured, film coated, oval shaped, biconvex faced tablets packed in aluminium foil strips in a box containing 24 strips of 10 tablets each.

**MANUFACTURER:** MACLEODS PHARMACEUTICALS LTD.

**ADDRESS:** Po. Box 401 404, Andheri (E), Mumbai - 400 059, INDIA.

**CLIENT:** Dr. Njee, P.O. Box 6750 - 00200, Nairobi.

**TEST(S) REQUESTED:** Dissolution Friability and Assay.

## RESULTS

<table>
<thead>
<tr>
<th>TEST</th>
<th>METHOD</th>
<th>COMPEIDIA</th>
<th>SPECIFICATION</th>
<th>DETERMINED</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformity of Weight</td>
<td>Weight</td>
<td>B.P. 2007 Vol IV App XVII G</td>
<td>≤ 2 tablets deviate by more 3% from mean</td>
<td>None Deviates</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Friability</td>
<td>Friability &amp; Weight</td>
<td>B.P. 2007 Vol IV App XVII G</td>
<td>≤ 1%</td>
<td>0.002%</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Friability</td>
<td>HPLC</td>
<td>USP 29 NF 24 Page 1922</td>
<td>No tablet less than 80%</td>
<td>Ethambutol: 101% (n=6; RSD=2.3%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rifampicin: 79.5% (n=6; RSD=3.9%)</td>
<td>DOES NOT COMPLY</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Isoniazid: 92.7% (n=6; RSD=1.7%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pyrazinamide: 95.6% (n=6; RSD=1.6%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Assay</td>
<td>HPLC</td>
<td>USP 29 NF 24 Page 1922</td>
<td>90.0 - 110.0%</td>
<td>Ethambutol: 103% (n=12; RSD=1.7%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rifampicin: 85.2% (n=12; RSD=1.8%)</td>
<td>DOES NOT COMPLY</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Isoniazid: 97.5% (n=12; RSD=1.9%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pyrazinamide: 101% (n=12; RSD=2.0%)</td>
<td>COMPLIES</td>
</tr>
</tbody>
</table>

**CONCLUSION:** The product failed to comply with the specifications for dissolution and assay of Rifampicin.

**ANALYST:** Mr. N. Bwey, DATE: 11/01/2008

**ANALYST:** Dr. S. Muthu, DATE: 11/01/2008

**ANALYST:** Dr. G. Wanganga, DATE: 11/01/2008

**DIRECTOR:** Dr. H. K. Chepkwony, DATE: 11/01/2008
### National Quality Control Laboratory

**CERTIFICATE OF ANALYSIS**

**CERTIFICATE No:** CAN/2008/008

<table>
<thead>
<tr>
<th>PRODUCT:</th>
<th>Rifampicin / Isoniazid / Pyrazinamide / Ethambutol Hydrochloride Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>REF. NO.</td>
<td>NDQ1220711478</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DATE RECEIVED:</th>
<th>30.11.2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>BATCH NO:</td>
<td>SL 794</td>
</tr>
<tr>
<td>MFG. DATE:</td>
<td>Jan. 2008</td>
</tr>
<tr>
<td>EXP. DATE:</td>
<td>Dec. 2008</td>
</tr>
<tr>
<td>CLIENT REF NO.</td>
<td>N(3)(a)</td>
</tr>
</tbody>
</table>

**LABEL CLAIM:** Each film coated tablet contains: Rifampicin U.S.P. 150 mg, Isoniazid U.S.P. 75 mg, Pyrazinamide U.S.P. 400 mg, Ethambutol Hydrochloride U.S.P. 275 mg.

**PRESENTATION:** Brown coloured, film coated, caplet shaped, bevelled faced tablets single scored on one face and plain on the other. Packaged in blister strips in a box carrying 8 strips of 20 tablets each.

**MANUFACTURER:** SVIZERA LABS.

**ADDRESS:** Mumbai, INDIA

**CLIENT:** Dr. Ngae, c/o Pharmacy and Poisons Board, P.O. Box 27663, NAIROBI.

**TEST(S) REQUESTED:** Dissolution Friability and Assay.

**RESULTS**

<table>
<thead>
<tr>
<th>TEST</th>
<th>METHOD</th>
<th>COMPENDIA</th>
<th>SPECIFICATION</th>
<th>DETERMINED</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformity of Weights</td>
<td>Weight</td>
<td>B.P. 2007 Vol. IV App XII G</td>
<td>≤ 2 tablets deviate by more than 2% from mean</td>
<td>None deviates</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Friability &amp; Weights</td>
<td>Friability &amp; Weight</td>
<td>B.P. 2007 Vol IV App XVII G</td>
<td>≤ 1%</td>
<td>0.005%</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Disolution</td>
<td>HPLC</td>
<td>USP 29 NF 24 Page 1922</td>
<td>No tablet less than 80%</td>
<td>Ethambutol: 98.6% (n=6, RSD=0.1%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rifampicin: 90.4% (n=6, RSD=0.9%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Isoniazid: 96.8% (n=6, RSD=1.9%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pyrazinamide: 97.6% (n=6, RSD=1.4%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Assay</td>
<td>HPLC</td>
<td>USP 29 NF 24 Page 1922</td>
<td>90.0 - 110.0%</td>
<td>Ethambutol: 101% (n=11; RSD=1.1%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rifampicin: 88.4% (n=8; RSD=1.4%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Isoniazid: 99.9% (n=10; RSD=1.9%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pyrazinamide: 99.6% (n=12; RSD=1.7%)</td>
<td>COMPLIES</td>
</tr>
</tbody>
</table>

**CONCLUSION:** The product fails to comply with the specifications for content of Rifampicin.

**ANALYST:** MR. N. BERGEN

**DATE:** 11/01/2008

**ANALYST:** DR. S. MUTERU

**DATE:** 11/01/2008

**ANALYST:** DR. G. WANG'ANGA

**DATE:** 11/01/2008

**DIRECTOR:** DR. H. K. CHEPKWONY

**DATE:** 11/01/2008
APPENDIX 5: CHROMATOGRAMS
FRIABILITY & DISINTEGRATION TEST FORM: TABLETS/CAPSULES

A: Friability Test.

<table>
<thead>
<tr>
<th></th>
<th>1st Run</th>
<th>Repeat</th>
</tr>
</thead>
</table>
| Total weight of 20 tablets before test (g) | 22.597661 | ✔
| Total weight of 20 tablets after test (g)   | 22.597551 | ✔
| Loss (g)                              | 0.00211 (g) | ✔

1st Run

\[
\text{%age loss} = \frac{\text{Loss (g)}}{\text{Total weight before test (g)}} \times 100 = 0.0092
\]

Repeat

\[
\text{%age loss} = \frac{\text{Loss (g)}}{\text{Total weight before test (g)}} \times 100 = 0.0092
\]

Comment:

B: Disintegration Test.

Disintegration Medium

Duration of Test (min)

Results observed:

Comments:

NQCI/WKS/2007/12/490