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TITLE

EVALUATION OF THE QUALITY OF CO-TIMOXAZOLE, PARACETAMOL AND PYRIMETHAMINE/SULPHADOXINE TABLETS MANUFACTURED BY LOCAL PHARMACEUTICAL MANUFACTURING COMPANIES IN LUSAKA

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT OF THE UNIVERSITY OF ZAMBIA FOR THE AWARD OF A MASTER DEGREE IN PUBLIC HEALTH

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DECLARATION

I hereby declare that the work presented in this study for the Master of Public Health has not been presented whether wholly or in part for any other study programme and is not being submitted for any other Masters programme. This work is entirely the result of my own independent investigation. The various persons and sources to which I am indebted are acknowledged.

Signed:.....

Date: 09/07/08

APPROVAL

This dissertation of Rabson Zyambo has been approved as fulfilling the requirements for the award of the Master degree in Public Health by the University of Zambia

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ABSTRACT

The production of substandard and counterfeit drugs as a result of non-adherence to good manufacturing practices by pharmaceutical companies is a vast and underreported worldwide problem particularly affecting developing countries. Developing countries are not only markets for substandard and counterfeit drugs, they also produce substandard and counterfeit drugs. Local pharmaceutical manufacturing companies in Zambia have not been spared from this vice. Counterfeit and substandard drugs have been associated with therapeutic as well as social and economic implications on the health of the individual, family, community and the nation at large. Unfortunately no research have been conducted in Zambia to determine the level of adherence to good manufacturing practices by local pharmaceutical manufacturing companies, hence this study.

Objective:

The purpose of this study was to assess the quality of co-trimoxazole, fansidar and paracetamol tablets manufactured in Zambia and to determine the levels of adherence to good manufacturing practices and factors contributing to non adherence to GMP by local pharmaceutical manufacturing companies in Zambia.

Study design:

A Cross Sectional Descriptive study was conducted. All six local pharmaceutical manufacturing companies authorized to manufacture drugs in Zambia were assessed for compliance to GMP. Samples of co-trimoxazole, paracetamol and pyrimethamine sulphadoxine tablets available at the time of sampling were obtained from each

pharmaceutical company provided they had a shelf life of at least three years. A sample was a sealed tin of 1000 tablets. The tablet were removed from their original containers and number coded before being taken to the Food and Drugs laboratory for analysis. However, the names, strengths, batch numbers, expiry dates and manufacturers' names were recorded. In total 126 co- trimoxazole, 126 paracetamol and 126 pyrimethamine sulphadoxine tablets samples were collected. A total of 10 members of staff at PRA were interviewed using a structured questionnaire. To compliment data from the GMP checklist and the questionnaire interviews were conducted to clarify certain issues.

Methods and materials:

Sample selection and collection

Selection of drug products in this study was based on their high usage and relevance to public health. Co-timoxazole, pyrimethamine/suphadoxine and paractamol tablets were chosen because they represent a relatively large proportion of the total drug usage and are all included in the Zambian essential drug list. Samples were collected from six local manufacturing companies. Drug quality was measured by level of active ingredient as percentage of stated content and by compliance (pass/fail) with assay standards of the British Pharmacopoeia volume (II) 1993. Adherence to GMP was measured by level of compliance (pass/fail) with standards of GMP outlined in GMP checklist.

Results: For active ingredients determination, all of the paracetamol and pyrimethathine/sulphadoxine samples tested gave values that complied with the B.P specifications except for co-trimoxazole The uniformity of weight determinations for all

the samples gave values which complied with the B.P specification for weight uniformity, as none of the samples deviated by up to 5% from the respective mean values. Similarly, the tablet hardness, friability, moisture and water content results for paracetamol and pyrimethamine/Sulphadoxine. The samples also complied with B.P specifications except for co-trimoxazole.

Conclusion: This study provides objective evidence to support frequent contentions that substandard drugs though in insignificant proportions are present in Lusaka. Drug sample marginally exceeded the B.P Pharmacopoeia limits on active ingredients content. Most likely these preparations are substandard not because of counterfeiting but as a result of absence of management control systems. This study showed a high degree of adherence to GMP by local pharmaceutical manufacturing companies in Lusaka.

DEDICATION

This research is dedicated to my wife Matildah for the love continuous support and encouragement

To my beloved children Gideon, Masuzyo, Tiza, Matipa and Mapalo for the inspiration that in a very special way kept me going.

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books i.e. British, European and United States Pharmacopoeia

Physical parameters - these include tablet hardness dissolution, disintegration rates, appearance and friability.

Quality - is the combination of attributes or characteristics of a product that determine the degree of acceptability and effecacy of the product.

Shelf Life - time taken from date of manufacture for the potency of the drug to fall to 90% of the label claim

Study Units - for the purpose of this study they refer to different types of drugs under study.

Substandard Drug - A drug with genuine packaging but with incorrect quantity of ingredients and not deliberately done (according to WHO definition).

ABBREVIATIONS

AIDS	Acquired Immuno- Deficiency Syndrome
B.P	British Pharmacopeia
CSO	Central Statistics Office
CTX	Co-trimoxazole Tablets
GMPs	Good Manufacturing Practices
HCl	Hydrochloric Acid
HIV	Human Immuno Deficiency Virus
HPLC	High Performance Liquid Chromatography
PCP	Pneumocystis Carinii Pneumonia
PRA	Pharmaceutical Regulatory Authority
QA	Quality assurance
SMX	Sulphamethoxazole
SOPs	Standard Operating Procedures
STIs	Sexually Transmitted Infections
TMP	Trimethoprim
UNZA	University of Zambia
URTIs	Upper Respiratory Tract Infections
USP	United States Pharmacopeia
UTH	University Teaching Hospital
UTIs	Urinary Tract Infections
U.V	Utra violet
WHO	World Health Organization

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CHAPTER ONE

1.0 INTRODUCTION

Zambia is a landlocked country with a landmass of 752,622 square kilometers (about 2.5 percent of Africa) and has population density of 13.7 people per square kilometer (CSO 2000). It shares borders with Democratic republic of Congo and Tanzania in the north; Malawi and Mozambique in the east; Zimbabwe and Botswana in the south; Namibia in the southeast and Angola in the west. Administratively the country is divided into nine provinces and 72 districts. Of the nine provinces, two are predominantly urban, namely Lusaka and coppeebelt provinces. The remaining provinces Central, Eastern, Northern, Luapula, North western, Western and Southern provinces are predominantly rural. Four 0ut of ten Zambians live in urban areas (Dzekezeke K. and Mulenga C. 2000).

The country has strived to improve the provision of social services to its people especially in health care. The government's commitment to the objectives of improving the quality of life of all Zambians has been demonstrated through its efforts to improve health care delivery through the health sector. In 1991, the Government of the Republic of Zambia articulated radical health policy reforms characterized by a move from a strongly centralized health system in which the central structures provided support and national guidance to the peripheral structures. An important component of the health policy reforms is the structured Primary Health Care (PHC) programme (Dzekezeke K. and Mulenga C. 2000).

The vision of the health reforms in Zambia was to "provide equity of access to cost-effective, quality health care as close to the family as possible (CBOH 2001).

An important component for a health care program is ensuring provision and availability of quality drugs in the health care facilities (Risha P.G et al.., 2003). Most pharmaceutical companies in Africa produce generic drugs. The introduction of generic drug products from multiple sources into the health care delivery system of many developing countries was aimed at improving the overall healthcare delivery systems in such countries. However, this has been accompanied by a variety of problems of which the most critical is the widespread distribution of counterfeit and substandard drug products (Adegbolagun O. 2007),

Drug quality has been a source of concern in a number of developing countries. There is a general feeling that there is a high incidence of drug preparations, which are not of the acceptable quality. Instances, which are quoted, are often linked with terms such as counterfeit and substandard which carry economic and perhaps political implications (Shakoor and Taylor, 2001). Poor quality drug preparations may lead to adverse clinical results both in terms of low efficacy, toxicities and predisposition to drug resistance.

A counterfeit drug is one that has been deliberately mislabeled for identity and/or source. It could be a perfect imitation containing the same active ingredients, same formulation, and identical packaging while a substandard product is a legally branded or generic

product, but one that does not meet international standards for quality, purity, strength, or packaging (WHO, 1999)

Counterfeit and substandard medicines are an insidious threat to global health, and the risks they pose have been largely underestimated to date. Apart from failing to cure disease, they can cause mental and physical damage and even death. Counterfeit and substandard drugs containing insufficient active ingredients breed resistance, which can make standard drugs useless. No area of the world is unaffected, but mounting evidence shows that the problem is disproportionately severe in developing and emerging-market countries, which also have the highest burden of infectious diseases.

Substandard drugs do not meet official standards for strength, quality, purity and/ or labeling. They may be legally registered innovator or generic products or counterfeits, which are deliberately mislabeled for identity, strength or source. Whether unintentionally substandard, drugs result in serious health implications such as treatment failure, adverse effects, increased morbidity, mortality, development of drug resistance and wastage of resources (WHO report 19999). They ultimately lead to an adverse public health problem

Potential contributing factors in production of substandard and counterfeit drugs include non adherence to Good Manufacturing Practices (GMP), greed, short cuts and desperations to cut costs by pharmaceutical manufacturing companies and lack of capacity by pharmaceutical regulatory boards to monitor these companies. The PRA was recently established in Zambia in 2006. However, at this early stage, its capacity to tackle problems of substandard and counterfeit drugs is unknown.

Globally, non-adherence to GMP accounts for 10% of the international trade in substandard and counterfeit drugs and 25% of medications used in the developing world, a particular problem where vulnerability factors include poverty and weaker regulatory systems (WHO report, 1999). In parts of Africa and Asia the prevalence of substandard and counterfeit drugs on the market as a result of non-adherence to GMP exceeds 50% representing annual sales in excess of US$ 35 billion (Jones R, FDA spokesperson, 2006).

Trade in counterfeit and substandard drugs, officially referred to as intellectual property piracy, negatively impacts our society through the loss of profits, jobs, revenue and poses risks to the community in both consumer safety through the sale of unsafe products and through the presence of criminal organizations responsible for the sale and distribution of those products (Judy, 2006). Counterfeits most often bring to mind designer handbags and brand-name foot apparel. Moreover, modern-day pirates counterfeit everything from life-saving drugs to cell phone batteries, from auto parts to computers, many posing serious threats to the welfare of buyers (Judy, 2006).

A review of literature by Shakoor and Taylor (2001) found that there was little data available, which point to the reasons for pharmaceutical products being substandard, majority of the literature reports contain anecdotal evidence and assume the products are counterfeits. However, no other reasons are given as to why substandard pharmaceutical products are produced apart from non-adherence to GMP.

In most developing countries, including Zambia, GMP is a concept that had received little attention even before the advent of drug resistance and treatment failure resulting from production of poor quality drugs. This has had a tremendous impact on the health budgets and service delivery of most governments in developing countries (WHO report, 1999). Counterfeit goods threaten security, economic growth and public safety worldwide. Of increasing concern, is the influx of counterfeit and substandard medicines into the marketplace (Rudolf and Bernstein, 2004). In Zambia, a report on working together to minimize health impact of new antimalarials showed that 38% of artesunate bought from South East Asia did not contain active ingredients (MMV access, 2006).

However, there is almost complete absence of quantitative data on the incidence of substandard drugs in Zambia. Moreover, production and the actual prevalence of substandard drugs in Zambia are unknown.

There are six pharmaceutical companies in Lusaka manufacturing antibiotics, antimalarials and analgesic agents like co-trimoxazole (CTX), pyrimethamine/sulphadoxine and paracetamol tablets as supplements to the ones imported from other countries. However, the extent to which these companies adhere to GMP is unknown.

This study aims at establishing an association between Adherence to Good Manufacturing Practice and drug quality.

1.1 BACKGROUND

The worldwide problem of incidence and prevalence of counterfeit and substandard drugs on the market is a major challenge to the Pharmaceutical Regulatory Authority in Zambia. The quality of medicines available in most less developed countries in general is inadequate in terms of content of active ingredients (Robert C et al., 2005). Therefore, knowledge of the extent to which pharmaceutical manufacturing companies adhere to GMP guidelines is important. However, in Zambia this is unknown as so far there have been no quality assurance mechanisms by the regulatory authority to monitor the performance of these companies.

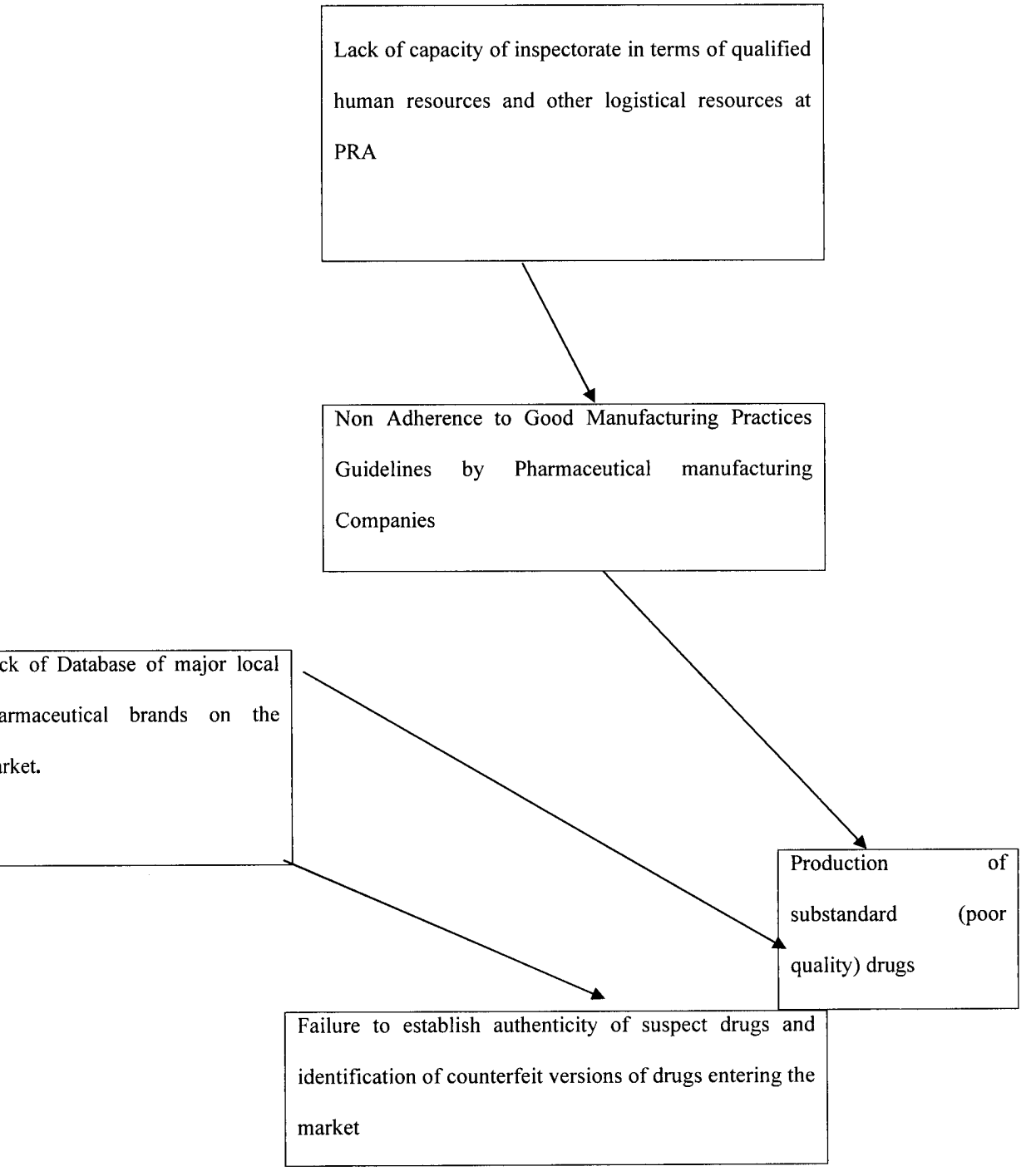
The production of substandard and counterfeit drugs as a result of non-adherence to good manufacturing practices by pharmaceutical companies is a vast and underreported worldwide problem particularly affecting developing countries (WHO report 1999). As such Pharmaceutical companies in Zambia cannot be absorbed of this vice. A situation analysis report of 1999, showed local production of pharmaceuticals in Zambia is an integral part of the National Drug Policy by providing quality, safe and efficacious drugs. To achieve this it was proposed that a medium sized National Drug Quality control Laboratory be setup within Zambia for independent pharmaceutical analysis as the Food and Drug Control laboratory did not appear to have adequate capacity for modern pharmaceutical analysis (Mutambo F et al., 1999). However, to date nothing has been done. The report further revealed that the pharmaceutical inspectorate was weak and ineffective and enforcement was poor. To date, despite establishment of the PRA, the capacity of inspectorate in terms of personnel and resource still remains unknown.

Substandard and counterfeit drugs have therapeutic, social and economic implications, all of which have great negative effects on the health of individuals, families and the community. The incidence and prevalence of substandard and counterfeit drugs appears to be rising and has not been adequately and synergistically addressed by close interaction between drug companies and authorities concerned with health and counterfeiting (Robert C et al., 2005). This, compromises the quality of health care services at all levels of the health care system. This has led to unnecessary morbidities, mortalities and loss of public confidence in the medicines and health structures in developing countries. According to anecdotal evidence, 1 out of 10 deaths worldwide is as a result of consumption of counterfeit or substandard drugs by the public. This may not be a true reflection of the existing problem because many cases go undetected (Fackler M 2002).

To solve the problem of producing substandard pharmaceutical products, attempts have been made by governments worldwide and the government of the republic of Zambia in particular to educate the public on the dangers of substandard and counterfeit pharmaceutical products and put up measures against the problem of availability and production of substandard pharmaceutical products. One such important measure has been to establish mini laboratories to detect substandard drugs at ports of entry. However, to date this has not been done (Mutambo F et al., 1999).

To ensure total compliance, quality assurance regulations on GMP have to be enforced by designated regulatory and quality control authorities in Zambia.

PROBLEM ANALYSIS



1.2 STATEMENT OF THE PROBLEM

The production of substandard and counterfeit drugs as a result of non-adherence to good manufacturing practices by pharmaceutical companies is a vast and underreported worldwide problem, particularly affecting developing countries (WHO report, 1999). It has continued for many years mainly in countries where vulnerability factors include poverty and weaker regulatory systems. This problem cannot be ignored especially in Zambia.

Developing countries are not only markets for substandard and counterfeit drugs, they also produce substandard and counterfeit drugs and as such pharmaceutical companies in Zambia could not have been spared from this vice. Although anecdotal evidence shows that 1 out of 10 deaths occurring in developing countries is as a result of consumption of substandard drugs by the public (Robert C et al., 2005). This may not be a true reflection of the existing problem because many cases go undetected.

Consequences of non-adherence to GMP are numerous and therefore, require quick solutions to stem this vice. Non-adherence to GMP results in production of substandard drugs. Poor quality drugs in general and analgesics, antibacterial and antimalarial agents in particular have therapeutic as well as social and economic implications on the health of the individual, family, community and the nation at large (Robert C et al., 2005).

Therapeutically, this might lead to development of resistance to drugs by microbes as well as treatment failure. In many cases, therapeutic failure is the only indication of substandard drugs. Besides the risk for therapeutic failure, degraded products or poor

quality drugs can produce sub-inhibitory concentrations in vivo, which lead to the development of resistant strains of microorganisms. Drugs that do not comply with minimum standards are illegal in all countries (Lasersan K et al., 2001) In addition; the quality of many antibiotics and other drugs in developing countries is often below standards prescribed in the official monographs and national formularies. This has resulted in loss of innocent lives.

Economically, treating infections resistant to first line drugs puts a lot of strain on the health budgets of governments as a lot of money is spent on the purchase of expensive alternative drugs. All drugs and medicines in general, should comply with the standards set in the official monographs. However, it is not known to what extent pharmaceutical manufacturing companies in Zambia comply with these requirements (Lasersan K et al., 2001).

Despite government's initiative to establish mini laboratories to detect such counterfeit and substandard drugs at ports of entry and attempts that have been made by the government of the republic of Zambia to educate the public on the dangers of substandard and counterfeit pharmaceutical products, the problem of proliferation and production of substandard pharmaceutical products seem to be on the increase (Mutambo F et al., 1999). To date the mini laboratories to detect such counterfeit and substandard drugs have been established but establishment of quality control laboratory is yet to be done. This study also aims at generating interest in establishing a quality

control laboratory to improve the process of determining compromised quality of pharmaceutical products.

Quality characteristics of drugs is assured through adherence to good manufacturing practices (GMP) in production, control and testing of drug products intended for investigational, commercial prophylactic or therapeutic use (Okeke and Robert,) According to report on adherence to GMP, many pharmaceutical companies in developing world do not follow GMP guidelines. If they do, the extent to which these companies comply with GMP is not known (Rago L, 2002).

1.3 JUSTIFICATION OF THE STUDY

Counterfeit and substandard medicines are an insidious threat to global health, and the risks they pose have been largely underestimated to date. Apart from failing to cure disease, they can cause mental and physical damage and even death. Counterfeit and substandard drugs containing insufficient active ingredients breed resistance, which can make standard drugs useless.

Globally, no single country is unaffected, but mounting evidence shows that the problem is disproportionately severe in developing and emerging-market countries, which also have the highest burden of infectious diseases ((WHO report, 2003).

There are several reports in Zambia of treatment failures with commercially available drug products. Despite several studies being done on different aspects of GMP compliance, most of the published work has been done outside Zambia. The effects of

consuming counterfeit and substandard drugs go unnoticed most of time, except in such cases where it results in mass deaths (WHO report, 2003). WHO estimate of 192 000 deaths as a result of counterfeit drugs in China is an indication of the scale of the the global problem. However, there is no reliable data on the mortality or morbidity arising from consumption of counterfeit or substandard drugs in Africa (Robert C et al., 2005). In Zambia such data is completely absent. More importantly there is an almost complete absence of quantitative data on incidence of substandard drugs in Zambia.

Counterfeits most often bring to mind designer handbags and brand-name foot apparel, but modern-day pirates counterfeit everything from life-saving drugs to cell phone batteries, from auto parts to computers, many posing serious threats to the welfare of buyers (Judy, 2006)

For the purpose of this study only legally registered local pharmaceutical manufacturing companies are being considered because they manufacture drugs that filter into both the private and public health system and have direct morbidity and mortality consequences. This study is significant because people's right to health include the right of access to quality drugs and assurance that drugs being consumed are not only genuine but also safe and effective.

Antibacterial (CTX) and antimalarial (fansidar) agents and an analgesic (paracetamol) have been chosen for this study because they represent a relatively large proportion of total drug usage and are all included in the WHO Model List of Essential Drugs. They are widely used to treat a variety of common bacterial infections, malaria and in management

of pain in Zambia. Although resistance does not appear to be happening at a large scale, quality of drugs such as co-trimoxazole is of great concern because no other drug has the same beneficial effects in prophylaxis and treatment of diseases such as Pneumocystis Carrnii Pneumonia.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 INTRODUCTION

Quality of pharmaceutical products is a major concern in both the developed and developing countries. Quality characteristics of drugs are assured through adherence to good manufacturing practices (GMP) in production, control and testing of drug products intended for investigational, commercial prophylactic or therapeutic use. GMP comprises that part of quality assurance aimed at ensuring that a product is consistently manufactured to a quality appropriate for its intended use. According to WHO report on GMP (1999), many pharmaceutical manufacturing companies follow guidelines as outlined by the WHO; however, it is the extent to which these companies adhere to GMP that is of major concern (WHO report, 2003)

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2.2 GLOBAL PERSPECTIVE

The production of substandard and counterfeit drugs as a result of non-adherence to good manufacturing practices by pharmaceutical companies is a vast and underreported worldwide problem, particularly affecting developing countries (Rudolf and Bernstein, 2004). It is an important cause of unnecessary morbidity, mortality and loss of public confidence in the medicines and health structures in developing countries (Robert C et al., 2005). The prevalence of substandard and counterfeit drugs appears to be rising and has not been adequately addressed by close interaction between drug companies and authorities concerned with health and counterfeiting (Rudolf and Bernstein, 2004).

Worldwide proliferation of poor quality and counterfeit drugs not only affects the quality of healthcare unfavorably; but it also confounds studies determining the effectiveness of commonly used pharmaceuticals to potentially resistant microorganisms. Globally, non-adherence to GMP accounts for 10% of the international trade in substandard and counterfeit drugs and 25% of medications used in the developing countries, a particular problem compounded poverty and weaker regulatory systems (WHO report, 1999).

A WHO (2003) survey in poor countries revealed that essential and life-saving drugs used to treat infectious disease such as tuberculosis and malaria are often the drugs under threat (WHO report, 2003). The burden of these diseases is greatest in these countries and there is often a frantic demand spurring the sale of counterfeit and substandard drugs on the market despite poor quality.

A research done in 2001 to determine causes of production of substandard pharmaceutical products showed that there was little data available which pointed to the reasons for pharmaceutical products, being substandard. Apart from short cuts and desperation to cut costs, majority of the literature reports contain anecdotal evidence and assume the products are counterfeits (Shakoor and Taylor, 2001). However, following studies (2004) showed that failure to control moisture content was a major contributing factor to poor drug quality.

Except in extreme circumstances like when a patient is comatose, tablets are favorably reliable vehicles for conveyance of medicament to the patient. During their production,

official monographs are desired to assure compliance to all parameters relating to drug quality (Bentley, 2003). Moisture content in pharmaceutical products should be of required standard as it is one of the major causes of drug degradation. Moisture content can also affect tablet hardness, friability, disintegration, and dissolution and product stability depending on the physio-chemical properties of the product. The most common drug degradation process is hydrolysis. In short, the rate at which this process progresses is highly dependent on the moisture content levels (Bentley, 2003).

Moreover, moisture content can also affect other tablets constituents such as binders thus affecting tablet performance in terms of disintegration and dissolution. An investigation on the fundamental effects of moisture on binders revealed that moisture content levels in the final tablet affects its performance (Joneja S et al., 2001). A study on correlation and prediction of moisture mediated dissolution stability for benazepril hydrochloride tablets showed a direct correlation between moisture content of benazepril hydrochloride tablets and their percentage dissolution (Li S et al., 2004).

In a cross sectional survey conducted in South East Asia (2002 to 2003) to assess the prevalence of counterfeit antimalarial drugs by measuring the proportion of the drug artesunate in antimalarial tablets it was found that, of the 188 tablet packs purchased which were labeled as artesunate, 53% did not contain any artesunate and 47% contained less active ingredients (WHO, 2001). Absence of active ingredients in the pharmaceutical product has been a major cause of mortality in many developing countries.

A WHO, (2000) survey on presence of poor drug quality reports from 20 countries showed that 60% of counterfeit medicines cases occurred in poor countries and 40% in industrialized countries. Of 771 reported cases of poor quality drugs 77% were from developing countries (WHO April 1999 database on counterfeits). Analysis of this data showed that in 60% of the 325 cases an active ingredient was missing while 40% contained less active ingredients (WHO, 2007).

Despite the WHO reported estimate of up to 25% of medicines consumed in developing countries being counterfeits or substandard, majority of these drugs are antimicrobials and antimalarials (Dalsgaard A et al., 2000).These drugs have become a particular favorite of the counterfeiters who prey upon the poor and ill-informed populace of the developing countries (Murray B et al., 1985).

A WHO concept paper on combating counterfeit drugs (2006) revealed that more than 40% of the world's population is at risk of malaria, antimalarial drugs have become a favorite target of counterfeiters (Rudolf and Bernstein, 2004). For example, counterfeit artemisinins are a significant problem in Southeast Asia and are expected to become a serious problem in Africa where artemisinin combination therapy is being implemented (Yeung S et al., 2004, Bruneton C et al., 2006). Because of widespread proliferation of counterfeit drugs, confirmation of good drug quality should be established prior to any efficacy or resistance studies. This is because drug quality, as well as the manner in which pharmaceuticals are used, contributes to development of drug resistance (Murray E et al., 1985, Bogaerts J et al., 1999).

2.3 REGIONAL PERSPECTIVE

In Africa statistics on prevalence of substandard drugs on the market may be scarce but the little that is known in developing countries is disturbing. In most developing countries, including Zambia, GMP is a concept that had received little attention even before the advent of drug resistance and treatment failure that result from production of poor quality drugs (Rudolf and Bernstein, 2004).

This has had a tremendous impact on the health budgets of most governments in developing countries (WHO report, 2001) as governments spend a lot of money to buy expensive alternative drugs. Counterfeit goods have continued to threaten security, economic growth and public safety in developing countries. Of increasing concern, is the increase in the number of counterfeit and substandard medicines entering the marketplace (Rudolf and Bernstein 2004, WHO, 2007).

A research conducted by Risha et al, 2003, on the quality of essential drugs on the Tanzanian market revealed that two out of the four tested sulfadoxine/pyrimethamine tablets failed to comply with the USP specification requirements for drug release i.e. dissolution and disintegration. In addition, further dissolution tests performed showed dissolution and disintegration failure of pyrimethamine in SP samples obtained from Africa (Vervaet C et al., 2002).

Furthermore, a multinational cross-sectional survey conducted on the prevalence of fake antimalarials in Nigeria, Tanzania and Uganda showed that most treatment failures were as a result of administration and availability of poor quality drugs to the general public (Dondorp A et al., 2004) In Nigeria for example, substandard ampicillin, ampiclox, tetracycline, and oxytetracycline capsules have been detected. In many cases, therapeutic failure is the only indicator of substandard drugs. Analytic laboratories to detect substandard drugs are uncommon, and when they exist, health workers, distributors, and consumers are often unaware of them (Shakoor and Taylor 2001).

A research conducted on quality of Phenobarbitone tablets in the urban community of Nouakchott (Mauritania) showed that out 60 samples analyzed 23% failed the B.P (1993) requirement for phenobarbitone tablet dissolution. Therefore, quality is a combination of attributes or characteristic of product that determines the degree of its acceptability. It depends on the care taken in its preparation by complying with GMP (Marie L et al., 2005).

According to a report by Fackler, (2002) failure to comply with GMP leads to production of pharmaceutical products of poor quality.

2.4 NATIONAL PERSPECTIVE

In Zambia the problem of availability of poor quality drugs to the public is an important and potentially dangerous phenomenon. In some cases these have been identified as the contributing factor to development of drug resistance by microorganisms. However, the Zambian policy on drug quality and the standard pharmaceutical practice (1995) advocate

for availability of drugs of acceptable standards to the general public at every point of administration. This can only be achieved by complying with GMP. Therefore, it is the responsibility of pharmaceutical companies to design, test and produce drugs that contain acceptable quantities of active ingredients because quality, purity, potency, stability, safety as well as biological availability and therapeutic activity are important characteristics of a drug.

According to the report of the Pharmaceutical Regulatory Authority (December 2006), mini laboratories to detect substandard drugs are in the process of being established. To date this has not been done.

Furthermore, according to a report on assurance and control of the attributes of product quality, there must be continuing search for causes of defects in pharmaceutical products and how to prevent them (Charkravarty and Ram 2001)

CHAPTER THREE

3.0 OBJECTIVES OF THE STUDY

3.1 GENERAL OBJECTIVE

- To assess the quality of co-trimoxazole, pyrimethamine/sulpadoxine and paracetamol tablets manufactured by local pharmaceutical manufacturing companies in Lusaka.
- To determine levels of adherence to GMP and factors contributing to non adherence to GMP by local pharmaceutical manufacturing companies in Lusaka.

3.2 SPECIFIC OBJECTIVES

3.2.1 To assess the capacity of inspectorate in terms of qualified human resources and other logistics at PRA

3.2.2 To assess the pharmaceutical companies adherence to GMP

- To determine the active ingredients in the study units
- To determine the percentage purity of the active ingredients in the study units
- To determine the physical parameters of the study units i.e. disintegration rate, friability, tablet hardness, moisture content and dissolution rate.
- To determine the stability of oral syrup preparations

3.2.3 To make recommendations to policy makers and law enforcement agents

CHAPTER FOUR

4.0 RESEARCH METHODOLOGY

4.10.1 INDENTIFICATION OF VARIABLE

Dependant Variables

Drug Quality

- Tablet Hardness
- Tablet Friability
- Disintegration Rate
- Dissolution Rate
- Moisture Content
- Active Ingredients

Independent Variable

Good Manufacturing Practice

Table 4.0.1: Variables and Indicators

Variables	**Indicators**	**Scale of measurement**
Tablet Hardness	Hardness	4.05 – 12.0kg/sq.cm
Disintegration rate	Disintegration	1 – 5 minutes
Dissolution Rate	Dissolution	Greater 75% of the active ingredients to go into solution within 60 minutes
Tablet Friability	Friability	Less than 1% loss of weight
Moisture content	Moisture	Less than 1% moisture content
Active ingredient content	Content	92.5 – 107.5% (Cotrimoxazole tablets) 95.0 – 105.% (Paracetamol tablets) 92.5 – 107.5% (Fansidar tablets)
GMP	Temperature Storage conditions Personnel qualification Suitability of premises Equipment	

4.1 STUDY DESIGN

A cross-sectional descriptive study was used. This design was used because it was suitable for determining the level of adherence to good manufacturing practices and factors that may contribute to non adherence to GMP.

This study focused on Local pharmaceutical manufacturing companies in Zambia because the study sought to describe their levels of adherence to GMP.

4.2 STUDY SETTING

The study was conducted in Lusaka district located in Lusaka province of Zambia. The assay analysis was done at Food and Drug laboratory in Lusaka.

4.3 STUDY POPULATION

The study population comprised of 64 x 1000s tablets co-trimoxazole, 64 x 1000s tablets fansidar and 64 x 1000s tablets paracetamol which were randomly selected from the six local pharmaceutical manufacturing companies in Zambia.

4.4 INCLUSION CRITERIA

Locally manufactured co-trimoxazole, pyrimethamine/sulphadoxine and paracetamol tablets with a shelf life of at least three years from the date of manufacture were used for the purpose of this study.

4.5 EXCLUSION CRITERIA

Co-trimoxazole, pyrimethamine/sulphadoxine and paracetamol tablets manufactured outside Zambia and locally manufactured co-trimoxazole tablets with a shelf life of less than three years from the date of manufacture.

4.6 SAMPLING PROCEDURE AND SAMPLE SIZE DETERMINATION

Samples of pyrimethamine/sulphadoxine, co-trimoxazole and paracetamol tablets were selected using structured systematic sampling of one in every 20-study units in every batch manufactured at the time of conducting this study. The study was designed to tolerate an absolute sampling error of up to 5 percent. The power of the study was 95 percent.

The following formula was used to calculate the sample size.

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

Where: -

Z = 1.96, the factor from the normal distribution

P = Expected period prevalence

d = Absolute sampling error

n = Sample size

Therefore $n = \frac{(1.96)^2 \times 50(100 - 50)}{5^2}$

= 384 tablets

However, since the pack unit is 10 x 1000, one tin of each of the study units was selected.

Since the study samples were collected from six pharmaceutical companies, the sample size from each pharmaceutical company was 64 comprising of 21 of samples of each drug under study.

4.7 DATA COLLECTION TECHNIQUES

Data was collected after carrying out the analysis of the study units following the laid down standard operating procedures (SOP) in the official monographs (B.P) 2003 and USP over a period of 12 weeks from date of approval. For GMP compliance assessment a standard checklist was used and structured questionnaire was used to obtain information on the strengths and weaknesses of the PRA. To make the research results more reliable interviews were conducted to support information from the questionnaire. It was hoped that the interviews would bring out issues that might not be obtained by questionnaire.

4.8 DATA QUALITY CONTROL CHECKS

The researcher in the presence of the Quality Control Manager and the Laboratory Instrumentation Manager at the Food and Drug laboratories did the monitoring of data quality immediately after each analysis.

4.9 DATA PROCESSING AND ANALYSIS

Data was entered and analyzed using Epi-INFO version 6 software. Prior to analysis, data was first entered on a spreadsheet for coding purposes. The completeness of the checklists for GMP compliance was checked whilst in the field. The questionnaires were given identification numbers and questions coded. This was then entered in the computer using the Epi data. Ranges and consistency checks were incorporated in the data entry program.

- Standard deviation was used to determine the acceptable values and association of adherence to GMP and the qualitative/quantitative variables (Tablet Hardness, Tablet friability, Disintegration Rate, Dissolution Rate and Moisture content)

4.10 ETHICAL CONSIDERATIONS

This study did not involve human subjects. However, clearance was sought from the Research Ethics Committee of the University of Zambia based in School of Medicine. Moreover, permission was sought from The Pharmaceutical Regulatory Authority and various pharmaceutical companies for their products to be used in this study. In addition, absolute care was taken to maintain confidentiality of information pertaining to products understudy during the process of data collection and analysis. For this the selected companies and study units were number coded

4.11 MATERIALS AND METHODS

4.11.1 Sample selection and collection

Selection of drug products in this study was based on their high usage and relevance to public health. Co-timoxazole, pyrimethamine/suphadoxine and paractamol tablets (**Table 4.11.1**) were chosen because they represent a relatively large proportion of the total drug usage and are all included in the Zambian essential drug list. Samples were collected from six local manufacturing companies.

Pyrimethamine/Suphadoxine tablet is an antimalarial agent, containing 500 mg N1-(5,6-dimethoxy-4-pyrimidinyl) sulfanilamide (sulfadoxine) and 25 mg 2,4-diamino-5-(p-chlorophenyl)-6-ethylpyrimidine [pyrimethamine] (B.P 1993). It is commonly used for the treatment of malaria as second line drugs and prophylaxis of malaria in pregnancy. Similarly trimethoprim/sulphamethoxazole tablets are a drug of choice in prophylaxis of PCP. The actions of the sulfadoxine and sulphamethoxazole components in tablets are due to their effects in potentiating the effect of pyrimethamine and trimethoprim respectively. These actions are presumably due to synergistic action at different stages of metabolic pathway during folate synthesis in the parasite (Michael O et al., 2003).

Table 4.11.1: Drugs and drug formulations chosen for the purpose of this study

Drug Class	Drug	Formulation
Antibacterial	Co-trimoxazole	Tablets
Analgesic	Paracetamol	Tablets
Antimalarial	Pyrimethamine/Sulphadoxine	Tablets

Drug quality was assessed by measuring level of active ingredient content as percentage of stated content in the sample tablets and compliance with B.P 1993 specifications for physical parameters tests. The assessment included chemical assay and carrying out uniformity of weight, friability, hardness, disintegration and dissolution tests on the sample tablets over a period of 12 weeks. Adherence to GMP was measured by level of compliance (pass/fail) with standards of GMP outlined in GMP checklist (appendix V).

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4.11.2 Assay

4.11.2.1 Paracetamol Tablets

Methods

Determination of the active ingredient percentage content in paracetamol tablets was quantitatively carried out by grinding 20 randomly selected tablets to a fine powder from which 0.15g were accurately measured and transferred into a 200.0 ml calibrated flask. A 50 ml volume of 0.1 m sodium hydroxide solution was added and the sample was shaken for 10 minutes, then 100 ml of distilled water were added and the sample shaken for a further 10 minutes. The solution was diluted to volume with distilled water, mixed and filtered and 5.0 ml of the solution was pipetted into a 500.0 ml calibrated flask. 50 ml of 0.1 m sodium hydroxide solution was added and the solution made to volume with distilled water. The absorbance was measured at 257 nm using 0.01M sodium hydroxide solution as a blank. The content of paracetamol was calculated taking 715 as the value of $A1\%$ 1 cm cell at the maximum at 257 nm using the formula A (1%, 1cm) = A/cd where A is the absorbance, c is the concentration of the absorbing solute expressed as %w/v and

d is the thickness of the absorbing layer. This method involved the measuring of absorbance of the active ingredients in solution.

4.11.2.2 Co-trimoxazole Tablets

Methods

Both sample and reference standard preparations were done according to the analytical procedures outlined in appendix vi.

4.11.2.3 Pyrimethamine/Sulphadoxine Tablets

Method:

Determination of the percentage content of pyrimethamine in pyrimethamine tablets was quantitatively carried out by grinding 20 randomly selected pyrimethamine/sulphadoxine tablets to a fine powder from which powder containing 25mg of pyrimethamine was accurately measured and transferred into a 200.0 ml calibrated flask. A 50 ml volume of hot 0.1M HCl was added and the mixture heated on a water bath for 10 minutes, swirling occasionally. The mixing was done with the help of the ultrasonic water bath for 30 minutes and thereafter cooled to room temperature. Sufficient 0.1 M was added to produce 100ml. this was filtered and 5ml of the filtrate was thereafter diluted to 100ml with 0.1m HCl. Absorbance of the resulting solution was measured at the maximum at 272nm. The content of pyrimethamine in pyrimethamine/sulphadoxine tablet was calculated using the formula outlined above under paracetamol tablets taking 316 as the value of A (1%, 1cm) at the maximum at 272nm. 0.1 m HCL was used in the reference cell.

4.11.3 Physical Parameters

For determination of the physical parameters of the study units the SOPs in the B.P (1993) were followed;

The disintegration times of the tablets were determined in distilled water at 37^0C using the Apex disintegration testing Apparatus (Apex Construction Ltd; Northflect Gravescent and Dartford, Kent, U.K). The disintegration time results were accepted only if the tablets disintegrate and go through the wire mesh.

For the tablets hardness test, twenty tablets from each formulation were tested for diametrical crushing test using the Monsanto hardness tester. Measurements were made in duplicates on individual tablets and the crushing strength results were accepted only if the samples split cleanly into two halves

The friability of the tablets was also determined using the Veego tablet friability apparatus at a speed of 25rpm for 5 minutes. Twenty tablets were weighed and subjected to abrasion. The tablets were weighed after five minutes and the weight compared to the initial weight.

For uniformity of weight determination; twenty tablets from each of the three tablet formulations was weighed individually using an electrical weighing balance. The average weights of the tablet were calculated as well as their percentage deviation from the mean weight. For tablet descriptions, the colour, shape and size were examined by visual observation

CHAPTER FIVE

5.0 DATA PRESENTATION

5.1 INTRODUCTION

The findings are from data that was obtained through analysis of study units obtained from six local pharmaceutical manufacturing companies, assessment of these companies adherence to GMP and Pharmaceutical Regulatory Authority capacities. Data was collected over a period of three months and is presented in way of cross tabulation. Tables; 5.2.1.1, 5.2.1.3, 5.2.2.1 and 5.2.3.1 provides information on the quality of the drug products, in term of content of active ingredients. Tables 5.2.1.4(a)(b), 5.2.2.2(a)(b) and 5.2.3.2(a)(b) provides information on the quality of the drug products in terms of physical parameters.

5.2 ANALYTICAL RESULTS

5.2.1 CO-TRIMOXAZOLE TABLETS

Table 5.2.1.1 shows mean values of TMP content in assayed Co-timoxazole tablet samples. Of the four assayed samples 1(25%) was not in compliance with B.P specifications (92.5 – 107.5% of the label claim amount). The amount TMP found in the assayed Co-trimoxazole tablet samples ranged from 100.3 to 116.9

Table 5.2.1.1 *Mean values of TMP content of Co-trimoxazole tablet samples expressed as a percentage of the labeled amount.*

Sample	Mass (g)	Mean drug content per tablet (mg)	Absorbance (A)	% of active ingredient content per tablet
A.	0.3872	82.8 ± 1.3	0.385	103.5%
B.	0.4065	83.4 ± 1.1	0.386	104.2%
C.	0.3905	93.6 ± 1.1	0.407	116.9%
D*	0.4019	80.2 ± 1.0	0.360	100.3%

D reference*

Mean drug content per tablet = 83.4 mg Standard Deviation = 6mg. Values accepted when ± 7% from the mean

Table 5.2.1.2 shows means values of SMX content in assayed Co-trimoxazole tablet samples. All the four assayed samples (100%) were in compliance with B.P specifications (92.5 – 107.5% of the label claim amount). The values of SMX content found in the assayed Co-trimoxazole tablet sample ranged from 97.8 to 102.6%.

Table 5.2.1.2: *means values of SMX content in assayed Co-trimoxazole tablet samples.*

Sample	Mean drug content Per tablet (mg)	% of the active ingredient content per tablet
A.	391.2 ± 1.5	97.8
B.	393.0 ± 1.5	98.2
C.	410 .4 ± 1.6	102.6
D*	398.3 ± 1.6	99.6

D reference*

Mean drug content per tablet = 398.0 mg Standard Deviation = 9mg. Values accepted when ± 2% from the mean

Table 5.2.1.3 Shows dissolution times and percentage content of SMX released from Co-trimoxazole tablets into solution within 60 minutes at pH 1.1 and temperature of 37.0 degree Centigrade. All the Co-trimoxazole tablet samples met the B.P specifications for dissolution (not less than 75% of the label claim amount should go into solution within 60 minutes).

Table 5.2.1.3:Dissolution *times and percentage content of SMX released from Co-trimoxazole tablets into solution within 60 minutes at pH 1.1 and temperature 37.0±2 degree Centigrade. Sampling Time 15 Minutes (limit: not less than 75% in Solution in 60 minutes).*

Sample	15min	30min	45min	60min	75min	90min
A	15.0	45.0	75.3	75.8	75.8	75.8
B	15.0	40.0	70.0	89.9	90.1	90.0
C	30.0	80.0	80.0	80.1	80.0	82.3
D*	20.0	35.0	65.0	85.7	88.1	88.0

G reference*

Table 5.2.1.4 (a) Shows mean values of physical parameters for Co-trimoxazole tablets. 1(255%) of four Co-trimoxazole tablets samples failed to meet B.P specifications for tablets hardness [4.05-12Kg/sq.cm], 3(75%) Co-trimoxazole tablets samples met B.P specifications for tablet friability [Less than 1% loss] and 1(25%) Co-trimoxazole tablets samples failed to meet B.P specifications for tablet moisture content [Less than 1%].

Table 5.2.1.4(a): *Values of physical parameters for Co-trimoxazole tablets*

Sample:	Tablet hardness	Tablet Friability (% loss)	Tablet Moisture content (%)
A.	10.0	0.9	1.0
B.	13.1	0.5	0.7
C.	4.9	5.4	1.3
D*.	13.9	0.2	0.6

D reference*

Table 5.2.1.4(b) Shows mean values of physical parameters for Co-trimoxazole tablets. 1(25%) Co-trimoxazole tablets samples did not meet the B.P specification for tablet water content (less than1% tablet water content. All (100%) Co-trimoxazole tablets samples met specification for tablet disintegration time (between 1- 5 minutes). The uniformity of weight determinations for all the samples gave values which complied with the B.P specification for weight uniformity, as none of the samples deviated by up to 5% from the mean value of 0.643g.

Table 5.2.1.4(b): *Values of physical parameters for Co-trimoxazole tablets*

Sample:	Tablet Water Content (%)	Uniformity of weight (g)	Tablet Disintegration time
A.	1.0	0.639	3 Min 53 Sec
B.	0.4	0.647	31 Sec
C.	1.1	0.647	40 seconds
D*	0.5	0.639	2 Minute

D reference*

5.2.2 PARACETAMOL TABLETS

Table 5.2.2.1 shows mean values of percentage of paracetamol content in assayed paracetamol tablet samples. All the assayed were in compliance with the B.P specifications (95.0 – 105% of the label claim amount). The amount of paracetamol found in the paracetamol tablet samples ranged from 94.2 to 99.4%.

Table 5.2.2.1: *Mean paracetamol content of different paractamol tablet samples expressed as percentage of the labeled amount.*

Sample	**Mean drug content Per tablet (mg)**	**Mass (g)**	**Abs (A)**	**% active ingredient content per tablet**
A	470.8 ± 5.7	0.1528	0.462	94.2%
B	476.2 ± 5.9	0.1533	0.470	95.2%
C	497.1 ± 5.6	0.1503	0.452	99.4%
D	457.8 ± 5.4	0.1511	0.454	91.6%
E	492.5 ± 5.7	0.1566	0.471	98.5%
F	488.2 ± 5.2	0.1519	0.454	97.6%
G*	488.1 ± 5.6	0.1522	0.458	97.6%

G reference*
Abs = Absorbance

Mean drug content per tablet = 481.5 mg Standard Deviation = 14mg. Values accepted when ± 3% from the mean

Table 5.2.2.2(a) Shows values of physical parameters for paracetamol tablets. All the paracetamol tablet samples were in compliance with the B.P specifications for tablets hardness [4.05-12Kg/sq.cm], tablet friability [Less than 1% loss] and tablet moisture content [Less than 1%]. All the samples gave a weight loss of less than the B.P specification of 1%w/w (Table 5.1.2.1). Also the mean crushing strength which is an

indication of the hardness of the tablets that brands B, E and G gave the highest crushing strength of 9.6, 7.9 and 8.1 kg/cm^2 and the moisture content was within the B.P specification of less than 1%.

***Table 5.2.2.2 (a)**: Values of physical parameters for paracetamol tablet samples*

Sample:	**Tablet hardness**	**Tablet Friability (% loss)**	**Tablet Moisture content (%)**
A	5.0	0.9	0.8
B	9.6	1.0	0.8
C	4.7	0.5	0.4
D	4.9	0.4	0.3
E	7.9	0.2	0.6
F	4.4	0.7	0.9
G*	8.1	0.2	0.4

G reference*

Table 5.2.2.2(b) Shows values of physical parameters for paracetamol tablets. All the paracetamol tablets samples were in compliance with B.P 1993 specifications for tablet water content (less than1% tablet water content and tablet disintegration time (between 1- 5 minutes). The uniformity of weight determinations for all the samples gave values which complied with the B.P specification for weight uniformity, as none of the samples deviated by up to 5% from the mean value of 0.553g.

Table 5.2.2.2(b) Values of physical parameters for paracetamol tablets

Sample:	Tablet Water Content (%)	Uniformity of weight (g)	Tablet Disintegration Time
A	0.9	0.562	3 minutes
B	1.0	0.554	3 Minutes
C	0.6	0.560	5 minutes
D	0.1	0.557	5 minutes
E	0.5	0.577	2 Minutes
F	1.0	0.553	3 min 56 sec
G*	0.9	0.573	4 minutes

G reference*

5.2.3 PYRIMETHAMINE/SULPHADOXINE TABLETS

Table 5.2.3.1 shows mean values of percentage of pyrimethamine content in assayed pyrimethamine/sulphadoxine tablet samples. All the assayed samples were in compliance with the B.P 1993 specifications (92.5 – 107.5% of the label claim amount) for pyrimethamine.

Table 5.2.3.1: *Mean pyrimethamine content of pyrimethamine/sulphadoxine tablet samples expressed as a percentage of the labeled amount*

Sample	Mass (g)	Mean drug content per tablet (mg)	Absorbance (A)	% of the active Ingredient content per tablet
A.	0.3728	84.5 ± 4.1	0.377	105.7%
B*	0.4020	81.0 ± 3.2	0.393	101.2%

B reference*

Mean drug content per tablet = 82.8 mg Standard Deviation = 2.5mg. Values accepted when ± 3% from the mean

Table 5.2.3.2(a) Shows values of physical parameters for pyrimethamine/sulphadoxine tablet samples. All the pyrimethamine/sulphadoxine tablet samples were in compliance with the B.P specifications for tablets hardness [4.05-15Kg/sq.cm], tablet friability [Less than 1% loss] and tablet moisture content [Less than 1%]. All the samples gave a weight loss of less than the B.P specification of 1%w/w (Table 5.2.3.2). Also the mean crushing strength which is an indication of the hardness of the tablets showed that samples A, F and G gave the highest crushing strength of 9.2, 8.9 and 10.1 kg/cm^2 and the moisture content was within the B.P specification of less than 1%.

Table 5.2.3.2(a): *Mean values of physical parameters for pyrimethamine/suphadoxine tablet samples*

Sample:	Tablet hardness	Tablet Friability (% loss)	Tablet Moisture content (%)
A.	9.2	0.1	0.4
B*	7.7	0.3	0.8

B reference*

Table 5.2.3.2(b) Shows values of physical parameters for pyrimethamine/sulphadoxine tablets. All the pyrimethamine/sulphadoxine tablets samples were in compliance with B.P 1993 specifications for tablet water content (less than1% tablet water content and tablet disintegration time (between 1- 5 minutes). The uniformity of weight determinations for all the sample gave values which complied with the B.P specification for weight uniformity, as none of the samples deviated by more than 5% from the mean value 0.553g.

Table 5.2.3.2(b) *Values of physical parameters for pyrimethamine/sulphadoxine tablets*

Sample:	Tablet Water Content (%)	Uniformity of weight (g)	Tablet Disintegration Time
A	0.2	0.558	5 minute
B*	1.0	0.572	2 min 35 sec

B reference*

5.2.4 COMPLIANCE TO GOOD MANUFACTURING PRACTICES

All the local pharmaceutical companies complied with good manufacturing practices outlined in GMP Checklist (appendix) except for other management controls which are not a requirement for GMP but have effects on the quality of the final pharmaceutical product e.g. quality assurance/quality control management controls, prioritization of workload, role definition, performance management and incentive systems. Three (50%) of pharmaceutical companies assessed did not have a formal system of workload prioritization, performance management and internal audit.

5.2.5 REGULATORY AUTHORITY CAPACITY

- At the time study was being conducted mini laboratories to detect the quality of drugs coming into the country were already established at ports of entry.
- There are plans to establish a medium drug quality laboratory by end of year 2010.
- Pharmaceutical Regulatory Authority has a database for major locally manufactured pharmaceutical brands
- Decentralization of the inspectorate function. Four regions have been proposed.

5.2.5.1 WEAKNESSES

- The Directorate of Inspectorate has a proposed structure of 17 people. .Of these 7 are supposed to be pharmacists and ten pharmacy technologists. These are to be based in four region, however, at the time of this study there were only 7 pharmacists in this directorate and all were based at PRA Secretariat.

- The Mini Laboratories can only detect quality of a limited number of drugs (i.e. the Mini Laboratories Database has a limited number of reference drugs).

CHAPTER SIX

6.0 DISCUSSION

This Cross Sectional Descriptive Study was conducted to assess the quality of co-trimoxazole, pyrimethamine/sulfadoxine and paracetamol tablets manufactured by local pharmaceutical manufacturing companies in Lusaka and to determine levels of adherence to GMP and factors contributing to non adherence to GMP by local pharmaceutical manufacturing companies in Lusaka. The results of this study (**Tables 5.2.1.1 to 5.2.3.2(b)** provide objective information on the quality of locally manufactured drugs in terms of active ingredients content, disintegration time dissolution, tablet hardness and friability of the co-trimoxazole, Paracetamol and pyrimethamine/Suphadoxine tablet samples from local pharmaceutical manufacturing companies. The findings confirm anecdotal reports on the incidence of poor quality drugs available to the general public. Of particular importance is the finding that 1(25%) of the Co-trimoxazole tablet sample assayed was not in compliance with B.P 1993 specifications for active ingredient percentage content (92.5 to 107.5%) and that the Mini Laboratories Database can only detect a limited number of reference drugs.

Quality can be defined as a combination of attributes of a product that determine its degree of acceptability as the right product for its intended use and exert the intended pharmacological actions. The quality of a pharmaceutical product depends on the degree of care taken in its preparation. The assay results on percentage content of active ingredients in the tablet samples shows that this parameter was within the specifications requirement of the B.P 1993 except for co-trimoxazole tablet samples.

The findings that 1 (25%) of the Co-trimoxazole samples failed to comply with B.P limits for TMP content and tablet friability and moisture content is suggestive of the fact that despite pharmaceutical companies complying with GMP requirements, there are other factors which are not complied with e.g. management control systems (i.e. internal audits in quality control and assurance, although these factors are not specifically required by GMP they do affect GMP compliance (Pharmaceutical Technology 2005). Even if there are no specific requirements for internal audits, a good internal audit will not only detect problems, but also advocate for which actions to take before products reach the market. Despite each pharmaceutical manufacturing company having its own approach and variations of philosophies, organization structures, and procedures for quality assurance program, the basic purpose of establishing such a program is the same. This is to ensure that products meet the required specifications outlined in the official monographs.

Tablet hardness is a non specific term routinely applied to several tablet parameters such as resistance to attrition or abrasion and crushing or impact strength. Tablets should have sufficient hardness to withstand the pressure during handling, packaging, dispensing and transportation. Although 2(50%) of the Co-trimoxazole samples failed to comply with the B.P specifications for tablet hardness, it was difficult to attribute this to lack of quality control or management control systems. Tablet hardness generally tends to increase with normal storage. However, it should always be within the required limits as it is one factor that greatly affects other tablet physical parameters such as dissolution and disintegration time. A study by Risha et al, 2002, on the quality of essential drugs in the Tanzanian market showed that two out of every four tested sulfadoxine/pyrimethamine tablets failed

the USP requirements for pyrimethamine dissolution and disintegration. This was largely attributed to failure by companies to establish in house management control system.

The findings that 1(25%) of Co-trimoxazole samples failed to comply with friability and tablets moisture content tests limits again was suggestive of lack of management control systems. This meant that the tablets were not going to withstand the multiple shocks which occur during handling, shipping and dispensing without capping lamination or chipping. Capping and chipping of tablets usually lead to loss of considerable amount of actives ingredients.

Moisture content in pharmaceutical products should be of required standard as it is one of the major causes of drug degradation. Moisture content can also affect tablet hardness, friability, disintegration, and dissolution and product stability depending on the physio-chemical properties of the product. Excess moisture accelerates the degradation processes of products. In case of Co-trimoxazole it could lead to hydrolysis of the ether bonds in trimethoprim thus converting it into a tricarboxylic acid compound that could either be toxic or ineffective. Moreover, moisture content can also affect other tablets ingredients such as binders thus affecting tablet performance in terms of disintegration, dissolution and effectiveness. An investigation on the fundamental effects of moisture on binders revealed that moisture content levels in the final tablet affect its performance. Joneja S et al., (2001).The findings of this study showed that samples with high moisture contents did not comply with the tablet friability test but had high dissolution and disintegration rates. The findings are similar to those obtained by Li S et al. (2004) on correlation and

prediction of moisture mediated dissolution stability for benazepril hydrochloride tablets. The study showed a direct correlation between moisture content of benazepril hydrochloride and their percentage dissolution.

All the local pharmaceutical companies complied to good manufacturing practices outlined in GMP Checklist (appendix) except for other management controls which are not factored within the protocols of GMP. However, they have effects on the quality of the final pharmaceutical product e.g. quality assurance/quality control management controls, prioritization of workload, role definition, performance management and incentive systems. An agreed upon system of workload prioritization ensures that time-sensitive tasks are accomplished on schedule. For example, if stability tests are performed by the same analysts who test batches for release to the market, lack of work prioritization may result in missed test intervals. An emphasis on timeliness results in the staff working to meet the time frame, giving priority attention to important investigations that are close to the time limit. One 1(16%) of pharmaceutical companies assessed did not have a formal system for workload prioritization, performance management and internal audit

The findings showed that the amount of active ingredients in the analyzed drug sample fell within recommended limits. This was suggestive that the drugs were not counterfeits but substandard as a result of lack of management control systems e.g. workload prioritization, performance management and internal audits. Substandard preparations have been attributed to poor manufacturing practices and this is consistent with findings

of the study on Assessment of the Incidence of Substandard Drugs in developing countries (Shakoor and Taylor, 2001).

Formal systems of workload prioritization ensure that time sensitive tasks are accomplished on schedule e.g. if stability testing is performed by same analysts who tests batches for release to the market, stability testing ends up taking a back seat resulting in missed test intervals. This is one of the major factors that contribute to offloading of poor quality drugs into the market. This is consistent with some of the findings of this study on the content of active ingredients in the drug samples.

At the time the study was being conducted mini laboratories to detect the quality of drugs coming into the country were already established at ports of entry. Of particular importance is the fact that plans are underway to establish a medium drug quality control and assurance laboratory by year 2010 and that the Pharmaceutical Regulatory Authority has a database for major locally manufactured pharmaceutical brands. This coupled with planned decentralization of the inspectorate function would lead to improved regulatory supervision and monitoring of pharmaceutical manufacturing companies in Zambia.

The Directorate of Inspectorate at PRA has a proposed structure of 17 people comprising of 7 pharmacists and ten pharmacy technologists to be based in four regions. However, at the time of this study there were only 7 pharmacists in this directorate and all were based at PRA Secretariat. This impact negatively, on the ability of the inspectorate to carry out its functions. The Mini Laboratories Database has a limited number of reference drugs.

The Mini Laboratories can only detect quality of a limited number of drugs. This does suggest that quality of most locally manufactured drugs is not monitored by PRA.

6.1 CONCLUSION

This study provides objective evidence to support frequent contentions that substandard drugs though in insignificant proportions are present in Lusaka. Samples of Co-trimoxazole tablets marginally exceeded the recommended B.P Pharmacopoeia limits on content of active ingredients. Most likely these preparations are substandard not because of counterfeiting but suggest absence of management control systems. This study showed a high degree of adherence to GMP by local pharmaceutical manufacturing companies in Lusaka. This shows that production of poor quality drugs is not only as a result of non adherence to GMP but could also be as a result of absence of other management systems like lack of formal systems on work prioritization and internal audits. Use of substandard drugs could have serious clinical consequences and implications on patients. The results support the need for strengthening the capacity of PRA. This will ensure continuous monitoring of the quality of drugs being manufactured in Zambia to ensure safety and efficacy of these products in the treatment and prophylaxis against diseases

6.2 RECOMMENDATIONS

This study's findings has established that substandard drugs are present in Lusaka though in insignificant proportions. This has serious and far reaching implications for the pharmaceutical industry if not checked.

It is in recognition of this that the following recommendations are made.

- PRA capacity should be strengthened in terms of human resource, financial support and transport.
- PRA hasten the process of decentralizing its operations to improve regulatory supervision and monitoring of pharmaceutical manufacturing companies.
- The number of reference drugs on the Mini Laboratories Database should be increased to allow it to detect quality of a large number of drugs. This will also allow quality of most locally manufactured drug to be assessed by PRA.
- PRA ensure that all pharmaceutical companies put in place management systems that enhance adherence to good manufacturing practices.

6.3 STUDY LIMITATIONS

- Despite six local pharmaceutical companies being legally registered to manufacture drugs with PRA, at the time of this study only four were registered to manufacture co-trimoxazole tablets and only one was registered to manufacture pyrimethamine/Sulphadoxine tablets.

- HPLC was not done to allow for the possible reasons to be assigned for any poor quality that could be detected.

8. Chakravarty S, Unnithan S, and Ram A (2001 January 29) Deadly doses. India today 56-61

9. Dalsgaard A, Mortensen HF, Molbak K, Dias F, Serichantalergs O Echeverria P et al. Molecular characterization of *Vibrio cholerae* O1 strains isolated during cholera outbreaks in Guinea-Bissau. J Clin Microbiol 2000; 34:1189-92.

10. David L. Advanstar communication, Pharceutical Technology (April 2005): 64 – 72.

11. Dondorp A et al., "Fake Antimalarials in Southeast Asia Are a Major Impediment to Malaria Control: Multinational Cross-Sectional Survey on the Prevalence of Fake Antimalarials," *Journal of Tropical Medicine & International Health* 9, no. 12 (December 2004): 1241-46.

12. Dzekezeke K. and Mulenga C. Zambia Population Census, Central Statistics Office 2000.

13. Fackler M 2002 July 29; The Global Threat of Counterfeit Drugs; Chinese Fake Drugs Kills Thousands San Francisco Examiner Plos Medicine.

14. Joneja SK, Harcum WW, Skinner GW, Barnum PE, Jian-Hwa G. Investigating the Fundamental effects of Binders on Pharmaceutical Tablet Performance, Drug Development and Industrial Pharmacy, Vol 25, Issue 10, 2001: 1129-1135

15. Judy Aita (2006) Counterfeit Drugs Seen as Growing Problem (Reports) U.S Mission to the European Union, New York office of the U.S. Immigration and Customs Enforcement agency.

Available at http://useu.usmission.gov/Article.asp?ID=192DAB5E-9A43-4354-9C0C-C5D5E97CF3FE (accessed June 12, 2007).

16. Lasersan KF, Kenyon AS, layloff T, Binkin NJ and Kenyon TA. Substandard Tuberculosis drugs on the Global Market and their Simple Detection, The International Journal of Tuberculosis and Lung Diseases Vol 5 No. 5: 2001; 449- 454 (7)

17. Li S, Wei B, Fleres S, Comfort Royce A. Correlation and Prediction of Moisture Mediated Dissolution stability for Benazepril Hydrochloride Tablets, Pharmaceutical Research, Vol 21, Number 4, 2004:617-624(8).

18. Marie L, Hamidou T, Louis B, Marie P, Mrylene VP. Quality of Phenobarbital Solid Dosage Forms in the Community of Nouakchott (Mauritania) The Epilepsia Vol 46 Issue 8:2005; 1293.

19. MMV access meeting report; working together to maximize the health impact of new antimalarials, Livingstone Zambia 6 May 2006.

20. Michael O, Olajire A, Remilekun B, Oluwatoyin A and Oludele O, Comparative analysis of eight brands of sulfadoxine-pyrimethamine tablets, *Tropical Journal of Pharmaceutical Research , Vol. 2, No. 1, June, 2003 pp. 161-167*

21. Mutambo F, Patidar G, Mmembe B, Kampamba RM, Local production of pharmaceuticals, Zambia National Drug Policy 1999; 10-11.

22. Murray BE, Alvarado T, Kim KH, Vorachit M, Jayanetra P, Levine MM et al. increasing resistance to trimethoprim-sulfamethoxazole among isolates of *Eschericha* coli in developing countries. J Infect Dis 1985; 147:724-8.

23. Okeke I N, Adebayo L and Robert Edelman. Socioeconomic and Behavioral Factors Leading to Acquired Bacterial Resistance to Antibiotics in Developing Countries Obafemi Awolowo University, Ile-Ife, Nigeria; and †University of Maryland School of Medicine, Baltimore, Maryland, USA

24. Rago L, Counterfeit drugs: Threat to public health [presentation], First Global Forum on Pharmaceutical Ant counterfeiting 2002 September 22-25, Geneva Switzerland.

25. Risha PG, Shewiyo D, Msami A, Musuki G, Vergote G, Vervaet C et al. In vitro evaluation of the quality of essential drugs on the Tanzanian market. Trop Med Int Health 2003; 7:701-7.

26. Robert C, Paul N, Agarko k, Akunyili D, Nicholas IW The Global Threat of Counterfeit Drugs: Why Industry and Governments Must Communicate the dangers, PLoS Medicine Public Library of Science 2005; Vol 2 Issue 4.

27. Rudolf PMM, Bernstein IBG Issues of Counterfeit Drugs N. Engl J Med (350) 2004; 1384-1386.

28. Shakoor O, Taylor RB, Behrens RH Assessment of the incidences of substandard drugs in developing countries: Tropical Medicine and International Health Vol 2 No. 9: 1997; 839-845.

29. Shakoor O, Taylor RB Quality of Co-trimoxazole Products in Nigeria, Thailand and Tanzania, Too Little, Too Much or More Dealing with Substandard and Fake Drugs Journal of Pharmacology Vol 357 Issue 9272: 2001; 1904.

30. Shakoor O, Taylor BB. Pharmacopoeia Quality of Drugs Supplied by Nigerian Pharmacies, Lancet the Science Direct Vol 357 Issue 9272 (2001); 1933-1936.

31. World Health Organization (WHO), "Combating Counterfeit Drugs: A Concept Paper for Effective International Cooperation" (concept paper, WHO, Rome, January 27, 2006), available at www.who.int/medicines/counterfeit_conference/en/index.html (Accessed May 30, 2007).

32. World Health Organization Department of Essential Drugs and Other Medicines (1999) Counterfeit drugs; Guidelines for the development of measures to combat counterfeit drugs. Geneva; World Health Organization.
Available; http*//whqlibdoc.who.int/hq/1999/WHO EDM QSM 99.1.pdf.*
Accessed 18 February 2005.

33. WHO, "Substandard and Counterfeit Medicines," fact sheet, November 2003, Available at www.who.int/mediacentre/factsheets/2003/fs275/en/ (accessed May 30, 2007).
Available from: http://www.who.int/mediacentre/factsheets/fs094/en/ (accessed Jan 2006)

34. World Health Organization (2001) Counterfeit drug reports 1999-October 2000[table] Available: **www.who.int/medicines/library/pneslet/pn300cfd.html**. Accessed 17 June 2003

35. Yeung S, Newton PN, Mayxay M, Van Damme W, Smithuis FM. Fake antimalarials in Southeast Asia are a major impediment to malaria control: Multinational cross-sectional survey on the prevalence of fake antimalarials. Trop Med Int Health 2004, 9: 1241-6.

APPENDIX II

IMPLEMENTATION PLAN

Table 4 Work Plan Gantt chart

escription f activities	Timeframe												Responsil person
	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	
esentation f research oposal													Principal Investigato
esentation f research oposal to hics ommittee													Principal Investigato
raining of esearch ssistants													Principal Investigato
ata ollection													Principal Investigato
ata nalysis													Principal Investigato
esearch eport riting/ bmission													Principal Investigato

APPENDIX III

Description	Responsible person	Daily Wage (K)	Number of personnel	Working Days per Week	Duration of Activity	Total Cost (K)
Personnel						
	Research Assistant	30,000.00	5	5	2weeks	1,500,000.00
	Principal Investigator	300,000.00	1	5	2weeks	1,500,000.00
	Research Statistician	300,000.00	1	5	2weeks	1,500,000.00
Supplies	Lab top					1, 300,000.00
	Photocopier					1,500,000.00
	Medical equipment					1,440,000.00
Travel	UTH to					

	Pharmaceutical companies and Ndola					1,500,000.00
Others	**Quantity**		**Unit Cost**	**Unit**		
Fansidar Tablets	23		40,000.00	1000		920,000.00
Septrin Tablets	23		28,000.00	1000		644,000.00
Paracetamol Tablets	23		18,000.00	1000		414,000.00
Ream of paper	03		80,000.00	Each		240,000.00
				GRAND TOTAL		**12,454,000.00**

APPENDIX IV

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

24th April 2007
The Director General
Pharmaceutical Regulatory Authority
Lusaka

U.F.S. The Head of Department
The University of Zambia
Community Medicine
Lusaka

Dear Sir/Madam,

RE: **PERMISSION TO CONDUCT A RESEARCH AT FIVE PHARMACEUTICAL MANUFACTURING COMPANIES IN ZAMBIA**

I am a student at the University of Zambia pursuing a Masters Degree programme in Public Health. Part II of the programme requires me to produce a dissertation over a period of three months.

My research topic is "**To determine the extent to which Zambian pharmaceutical manufacturing companies adhere to good manufacturing practices.**

I am therefore requesting your kind office to grant me permission to conduct my research in the pharmaceutical manufacturing companies that will be randomly selected.

Your favourable response and assistance will be highly appreciated.

Yours sincerely

Rabson Zyambo

APPENDIX V

	GOOD MANUFACTURING PRACTICE (GMP) *CHECK LIST*			
ACTIVITY	***QUESTION***	**YES**	**NO**	**REMARK**
1.0 General Controls	1. Does the facility audit departments (organizational units) operate in a state of control as defined by the GMP regulations?			
1.1 Organizational & Management Responsibilities				
	1. Does this facility/business unit operate under a facility or corporate quality policy? 2. Does a Quality Assurance unit (department) exist as a separate organizational entity?			
	3. Does the Quality Assurance unit alone have both the authority and responsibility to approve or reject any components, drug product containers and closures, in-process materials, packaging materials, labeling and drug products?			
	4. Does the QA department or unit routinely review production records to ensure that routine QA procedures were followed and properly documented?			
	5. Are adequate laboratory space, equipment, and qualified personnel available for required testing?			
	6. If any portion of testing is performed by a contractor, has the Quality Assurance unit inspected the contractor's site and verified that the laboratory space, equipment, qualified personnel and procedures are adequate?			
	7. Date of last			

	inspection:			
	8. Are all QA procedures in writing?			
	9. Are all QA responsibilities in writing?			
	10. Are all written QA procedures current and approved? (Review log of procedures)			
	11. Are the procedures followed? (Examine records to ensure consistent record-keeping that adequately documents testing.)			
	12. Are QA supervisory personnel qualified by way of training and experience?			
	13. Are other QA personnel, e.g., chemists, analysts, laboratory technicians) qualified by way of training and experience?			
1.2 Document Control Program				
	1 Does the QA unit have a person or department specifically charged with the responsibility of designing, revising, and obtaining approval for production and testing procedures, forms, and records?			
	2. Does a written SOP, which identifies how the form is to be completed and who signs and countersigns, exist for each record or form?			
	3. Is the production batch record and release test results reviewed for accuracy and completeness before a batch/lot of finished product is released?			
1.3 Employee Orientation, Quality Awareness, and Job Training				
	Circle the types of orientation provided to each new employee: (1) Company brochure (2) Literature describing GMP regulations and			

	stressing importance of following instructions. (3) On-the-job training for each function to be performed (before the employee is allowed to perform such tasks). (4) Other: enter in notebook.			
	2. Does each employee receive retraining on an SOP (procedures) if critical changes have been made in the procedure?			
	3. Indicate how on-going, periodic GMP training is accomplished.			
	4. Is all training documented in writing that indicates the date of the training, the type of training, and the signature of both the employee and the trainer?			
	5. Are training records readily retrievable in a manner that enables one to determine what training an employee has received, which employees have been trained on a particular procedure, or have attended a particular training program?			
	6 Are GMP trainers qualified through experience and training?			
	7. Are supervisory personnel instructed to prohibit any employee who, because of any physical condition (as determined by medical examination or supervisory observation) that may adversely affect the safety or quality of drug products, from coming into direct contact with any drug component or immediate containers for finished product?			
	8. Are employees required to report to supervisory personnel any health or physical condition that may have an adverse effect on drug product safety and purity?			
	9. Are temporary employees given the same orientation as permanent employees?			
	10 Are consultants, who are hired to advise on any aspect of manufacture,			

	processing, packing or holding, of approval for release of drug products, asked to provide evidence of their education, training, and experience?			
	11 Are written records maintained stating the name, address, qualifications, and date of service for any consultants and the type of service they provide?			
1.4 Plant Safety and Security				
	1. Does this facility have a facility or corporate safety program?			
	2. Are safety procedures written?			
	3. Are safety procedures current?			
	4. Do employees receive safety orientation before working in the plant area?			
	5. Is safety training documented in a readily retrievable manner that states the name of the employee, the type of training, the date of the training, and the name of the trainer and the signature of the trainer and the participant?			
	6. Does this facility have a formal, written security policy?			
	7. Is access to the facility restricted?			
	8. Describe how entry is monitored/restricted:			
	9. Is a security person available 24 hours per day?			
1.5 Internal Quality/GMP Audit Program				
	1. Does this business unit/facility have a written quality policy?			
	2. Is a copy of this quality policy furnished to all employees?			
	3. If "yes" to above, when provided? _____			
	4. Is training provided in quality improvement?			
	5. Does a formal auditing function exist in the Quality Assurance department?			

	6. Does a written SOP specify who shall conduct audits and qualifications (education, training, and experience) for those who conduct audits?			
	7. Does a written SOP specify the scope and frequency of audits and how such audits are to be documented?			
	8. Does a written SOP specify the distribution of the audit report?			
2.0 Facility Control				
	(a) Are all parts of the facility constructed in a way that makes them suitable for the manufacture, testing, and holding of drug products? (b) Is there sufficient space in the facility for the type of work and typical volume of production? 2 Does the layout and organization of the facility prevent contamination?			
3.Environmental Control Program				
	1 The facility is NOT situated in a location that potentially subjects workers or product to particulate matter, fumes, or infestations?			
	2 Are grounds free of standing water?			
	3 Is lighting adequate in all areas?			
	4 Is adequate ventilation provided?			
	5 Is control of air pressure, dust, humidity and temperature adequate for the manufacture, processing, storage or testing of drug products?			
	6 If air filters are used, is there a written procedure specifying the frequency of inspection and replacement?			
	7 Are drains and routine cleaning procedures sufficient to prevent standing water inside the facility?			
	8 Does the facility have separate air handling systems, if required, to			

	prevent contamination? (MANDATORY IF PENICILLIN IS PRESENT!)			
4. Facility Maintenance and Good Housekeeping Program				
	1 Is this facility free from infestation by rodents, birds, insects and vermin?			
	2 Does this facility have written procedures for the safe use of suitable, (e.g. those that are properly registered) rodenticides, insecticides, fungicides, and fumigating agents?			
	3 Is this facility maintained in a clean and sanitary condition?			
	4 Is sewage, trash and other refuse disposed of in a safe and sanitary manner (and with sufficient frequency?)			
5 Equipment Control				
	1 Is all equipment used to manufacture process or hold a drug product of appropriate design and size for its intended use?			
	2 Are the following pieces of equipment suitable for their purpose? Blender(s), Conveyor(s), Tablet, Presses, Capsule Fillers, Bottle Fillers, Other (specify).			
	3 Are the following pieces of equipment suitable in their size/capacity? Blender(s), Conveyor(s), Tablet, Presses, Capsule Fillers, Bottle Fillers, Other (specify).			
	4 Are the following pieces of equipment suitable in their design? Blender(s), Conveyor(s), Tablet, Presses, Capsule Fillers, Bottle Fillers, Other (specify)			
	5 Are the locations in the facility of the following pieces of equipment			

	acceptable? Blender(s), Conveyor(s), Tablet, Presses, Capsule Fillers, Bottle Fillers, Other (specify).			
	6 Are the following pieces of equipment properly installed? Blender(s), Conveyor(s), Tablet, Presses, Capsule Fillers, Bottle Fillers, Other (specify)			
	7 Is there adequate space for the following pieces of equipment? Blender(s), Conveyor(s), Tablet, Presses, Capsule Fillers, Bottle Fillers, Other (specify)			
	8 Are machine surfaces that contact materials or finished goods non-reactive, non-absorptive, and non-additive so as not to affect the product?			
	9 Are design and operating precautions taken to ensure that lubricants or coolants or other operating substances do NOT come into contact with drug components or finished product?			
	10 Is each idle piece of equipment clearly marked "needs cleaning" or "cleaned; ready for service"?			
	11 Is equipment cleaned promptly after use?			
	12 Is idle equipment stored in a designated area?			
6 Measurement Equipment Calibration Program				
	1 Does the facility have approved written procedures for checking and calibration of each piece of measurement equipment? (Verify procedure and log for each piece of equipment and note exceptions in notebook with cross-reference.)			
	2 Are records of calibration checks and inspections maintained in a readily retrievable manner?			

7 Material/Component Control				
	1 Are incoming material and components quarantined until approved for use?			
	2 Are all materials handled in such a way to prevent contamination?			
	3 Are all materials stored off the floor?			
	4 Are materials spaced to allow for cleaning and inspection?			
	5 Are labels for different products, strengths, dosage forms, etc., stored separately with suitable identification?			
	6 Is label storage area limited to authorized personnel?			
	7 Are rejected components, material, and containers quarantined and clearly marked to prevent their use?			

Note: if answer is yes enter Y and if not enter N

Y = 1 and N = 0