DOCTOR OF PHILOSOPHY

The Evaluation and Analysis of Counterfeit Pharmaceuticals within Jordan

Alqatamin, Shatha Merthi

Award date:
2012

Awarding institution:
Coventry University

The Evaluation and Analysis of Counterfeit Pharmaceuticals within Jordan

Shatha Al-Qatamin

***A thesis submitted in partial fulfilment of the University's requirements for the Degree of Doctor of Philosophy* in Pharmaceutical Sciences**

Coventry University

2012

Acknowledgements

It is my pleasure to thank all individuals and institutions whose help and support made this thesis possible.

I would like to thank my supervisor in Coventry University Mr. Andrew Reid for the significant help, advice and helpful suggestions that had made my work at this quality. Special thanks to my co-supervisor Dr. Valerie Cox for her concern and follow up during my studies, which made this work possible.

I am extremely grateful to my supervisor in Jordan Dr. Adnan Badwan the general director of (JPM) for his guidance, encouragement, and important input throughout this thesis.

I would like also to thank the Jordanian Pharmaceutical Manufacturing Company (JPM) for their support by facilitating the use of labs, instruments and materials required to accomplish the analysis and investigation.

Special thanks should be conveyed to the staff of JPM research and development, Quality Control and excipient laboratories Departments whose help had been proven significant.

Finally, I would like to thank all members of my family who supported me throughout my journey: my father for believing in me and financially supporting me, to my husband Ahmed for his help during sample collections, and his encouragement and support throughout my work, and to my kids Addi, Hala, Dana and Alaa for their enthusiasm, support and encouragement which helped me significantly to complete this work.

Abstracts

The objective of this study was to evaluate the status of the counterfeit pharmaceuticals in Jordan. Four types of pharmaceuticals Lipitor (Atorvastatin-calcium), Concor (bisoprolol fumarate), Co-Diovan (Valsartan, hydrochlorothiazide) and Plavix (clopidogrel) were subjected to physical and chemical analysis. 173 samples of these four medicines were collected from the three most populated cities in the country, namely Amman, the capital of Jordan, Zarqa and Irbid. A sample of confiscated counterfeited medicines was obtained from the health authorities and tested utilising the HPLC and dissolution testing, in order to validate the reliability of the testing procedures. Samples were then tested using High Performance Liquid Chromatography (HPLC) and dissolution tests in order to assess the quality of these samples.

Results of both chemical and physical analyses revealed that all samples were found to fall within the specification limits of United States Pharmacopoeia (USP) and no evidence was found of any counterfeit drug products in the samples examined.

Since this study found no indication of a drug counterfeiting problem in Jordan, the researcher has concluded that there seemed to be two contributing factors to this result: first, the very effective legislative campaigns conducted by the health authorities' in Jordan against counterfeit trade through new public health and pharmacy law which has been launched in 2008. Second, the rigorous tough enforcement measures conducted by health and law enforcement agencies in the country.

Contents

Chapter One Introduction

Contents **Page**

Contents Page

Chapter Three Sampling Methodology

Chapter Four Analytical Methodology

Contents Page

Contents Page

List of Tables

Name — Page

List of Tables

Name — Page

List of Figures

Name Page

Abbreviation	Name
DMRC	Defective Medicines Report Center
EPC	electronic product code
FDA	United States Food and Drug Administration
JFDA	Jordan Food and Drug Administration
GMP	Good Manufacturing Practices
HPLC	High Performance Liquid Chromatography
HPLC-UV	High Performance Liquid Chromatography with UV detection
HPLC- DAD	High Performance Liquid Chromatography with diode array Detection.
LDL	Low density lipoprotein.
MHRA	Medicines and Healthcare Products Regulatory Agency
NIR	Near Infrared Spectroscopy
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IMPACT	International Medical Products Anti-Counterfeiting Task Force
IR Spectroscopy	Infrared Spectroscopy
PSI	pharmaceutical security institute
RAS	Rapid Alert System
RFID	Radio Frequency Identification
TLC	Thin Layer Chromatography
TRIPS	Trade-Related Aspects of Intellectual Property Rights
USP	United States Pharmacopoeia
WHO	World Health Organisation

CHAPTER ONE

INTRODUCTION

Chapter One

1.1. Introduction

Public health and the quality of medicine are both considered to be a main concern for health organisations worldwide and health authorities within countries.

During the last decade, counterfeit pharmaceuticals have generated global concern about their efficacy and the threat they cause to the health of the public.

During the same period, a new form of unregulated pharmaceutical trade gave the chance for imitated brand pharmaceuticals to appear in the market place. Consumers may use such products with their full belief that they are using the original brand while in fact they constitute a form of counterfeit pharmaceuticals.

Background information about the country of Jordan is provided in Appendix (A).

1.2 Health System and Counterfeit Pharmaceuticals Situation in Jordan

Following sections present detailed information about health system and counterfeit pharmaceutical elements in Jordan.

1.2.1 Pharmaceutical Distribution System in Jordan

For imported medicines, the JFDA along with the Ministry of Health (MOH) are responsible for the registration and authorisation of the medicine, which enters the country through a long process that includes obtaining pedigree papers from the pharmaceutical manufacturer, and a certificate of pharmaceutical product (CPP) from the country of origin. Trained inspectors are being sent to these manufacturers to make sure that they are in

compliance with the good manufacturing practices. Finally, health authorities are also required to evaluate the price of the medicine in order to be sure the price is compatible with price levels in the region.

Once the medicine is approved and registered for use then the wholesaler can import it from the supplier. A random sample of every batch is usually selected to be subjected to JFDA laboratory analysis. The objective of this analysis is to assure that all shipment batches are free of problems related to safety of the medicine, which is considered as a proof of complying with specifications. Once positive results of drug samples are obtained the wholesaler is allowed to distribute the medicine directly to the pharmacies or public and private hospitals.

In Jordan, the drugstore is any pharmaceutical institution engaging in importing, purchasing, selling, storing or distributing of drugs to pharmacies (Royal Decree 2001).

Import of drugs to the country is normally conducted by a drugstore, which is acting as an agent for the originator.

Once the medicine is approved and registered for use then the agent can import it from the supplier. Usually for each product, there is only one agent who is legally allowed to import the product after obtaining all required registration and authorisation requirements of the JFDA. This might explain the fact that parallel trade does not exist in Jordan because only the authorized wholesalers (agents) can import the product and other routes of importing are considered illegal, and shipment is subjected to confiscation and fines.

There are twelve districts in Jordan; each district has its own inspectors. The inspector is usually any pharmacist authorized for inspection by health regulatory authorities. Inspectors assume the responsibility of securing the proper compliance of public and private pharmacies with standards, such as expiry dates or illegal drug sale and drug recall activities. Another level of inspection is done by inspectors from the headquarters of JFDA in Amman who are assigned to perform unexpected visits to any district in the country.

There are two types of inspections usually conducted by JFDA:

- Routine inspections, which take the form of unannounced visits to all public and private pharmacies.
- Inspections following a complaint or a suspected behavior. This inspection is usually done by health inspectors accompanied with police officers especially if the complaint is related to a serious incident.

1.2.2 Counterfeit Trade Routes in Jordan

According to health authorities, counterfeit pharmaceuticals used to enter into the country through the following routes:

- Smuggling through the borders without passing customs by avoiding the regular passage of entry.
- Importing through regular borders depending on the high quality of packaging, which can deceive the customs authorities.

- Another source of counterfeiting is not through importation. Counterfeiters do sometimes manufacture their products locally without authorisation.

It seems that drug regulatory authorities acted and corrected the problem that involved these pharmaceuticals. For example, authorities have acted decisively by closing ten pharmacies in 2006 and sixty-one pharmacies in the year 2007 for selling counterfeit products (Sabag 2008).

Recently, new legislation was enacted to increase penalties for counterfeit pharmaceutical traders, and counterfeit drugs were defined for the first time, as detailed in Appendix (C).

Article number 65 stated that:

If the person convicted by buying or selling or exporting counterfeit medicine to the kingdom, he will spend a period not less than 3 years and not more than 5 years in prison with hard work, or the convicted individual will pay a fine not less than JD 1000, and not more JD 5000, or both penalties. In some serious circumstances, the fine will be twice as much as the price of the confiscated counterfeit drug (JFDA 2008).

1.2.3Status of Counterfeit Pharmaceuticals in Jordan

In Jordan, the health authorities reported many cases of confiscated counterfeited drugs in the last several years (Zyiadat 2009), the majority of them are drugs classified as life saving medications. In the last several months, cases of confiscated counterfeit drugs have been reported by JFDA (Jordan Food and Drug Administration) and several pharmacies were closed for dealing with the counterfeit drugs trade. Since there has been no formal research done to investigate this problem in the country, this study's main goal is to evaluate the nature and magnitude of the counterfeit problem in Jordan. If results indicate the presence

of a significant counterfeit problem, this research will help health authorities and law enforcement agencies in their fight against counterfeit drugs.

The JFDA estimated the value of smuggled and counterfeit medicines seized in Jordan during the year 2007 was around JD 10 million, equaling 2% of the volume of the general consumption of imported medications, which stood at JD 191 million in the same year. Another source, the head of Jordan Pharmacists Association (JPA) reported that a value of about JD 12 million was confiscated in 2007. This phenomenon has increased to the point where the JFDA has closed down 56 pharmacies for periods not exceeding one month in the year 2007, compared to 10 in 2006, and only one pharmacy in 2004, for selling smuggled and counterfeit drugs (Halteh 2008).

A daily local newspaper addressed the problem of counterfeiting in Jordan, which reported the closing down of 180 pharmacies after seizing counterfeit medications. The General Manager for JFDA said that they have confiscated medications worth approximately JD 17 million (Halteh 2008).

In June 2009, a workshop conducted by the JFDA was held near the Dead Sea to inform the media about the situation regarding counterfeit medicines and other issues related to pharmaceuticals as well as food issues.

It has been reported that the chief inspector at JFDA has announced that 33 pharmacies have been closed between January and June for different illegal practices; among these five were closed for dealing with counterfeit pharmaceuticals.

It has been reported also that a decline in the number of cases regarding this issue was noticed, due to the implementation of new public health laws, which applies more severe penalties than before (Zyiadat 2009).

1.3 Regional Counterfeit Situation

The following section presents the counterfeit situation in some neighboring countries:

1.3.1 In Saudi Arabia, Arab Consumer and Brand Protection Forum was held in Jeddah on May 9, 2009 and legal bodies agreed to step up legal actions to protect intellectual property; the emphasis was in combating counterfeit medicine since the kingdom is affected by this trade. One of the participants who was a director for a pharmaceutical manufacturer said that 30-40% of the medicine in the market is counterfeited and legal action should be considered to stop this trend. The president of the Jordanian Judicial Council and the head of Cassation Court mentioned in the same forum that Jordan has been struggling for years to protect brand names through its judiciary system, and recently they enacted more than 30 laws to combat piracy and establishing an ongoing training programme for judges and judiciary employees to comply with national and international legislations against piracy and counterfeit (Al- Iryani and Ba-swaid 2009).

1.3.2 In United Arab Emirates, Emirates is considered to have a very important location as a trade route specifically Dubai, which has a strategic location on the gulf between Asia, Europe and Africa. Dubai has been considered the place where one third of all counterfeit medicines confiscated in Europe in 2006 passed through. Smugglers make use of the fact that a huge amount of goods is usually moving through Dubai free trade zones. In these free trade zones, goods are normally passed through without tariffs and with a minimal regulatory oversight. Free trade zones allow the counterfeiters to avoid being rigorously inspected (Bogdanich 2007).

Authorities announced that they have seized a large amount of counterfeit medicines from Euro Gulf's warehouses, which were located inside the free trade zone in Dubai.

The investigation revealed that the route of a complex supply chain of counterfeit drugs came from China through Hong Kong, the UAE, Britain and the Bahamas and finally to the Internet pharmacy whose customers believed that they were buying from Canada. This Investigation shows that this illegal trade follows complex, sophisticated and hard to trace routes (Walt 2007).

1.3.3 In Iraq, another neighboring country to Jordan, the situation was deteriorating since the invasion of Iraq in 2003. There is always a lack of the most important medication and a need to find it and all kind of medicines are in a severe shortage especially antibiotics and life saving medication such as anti diabetes medicines, medicine for cardiovascular diseases and cancer medications which create the need to find these medications regardless of the

source. This has proven to be a great opportunity to the unauthorised medication to enter the country especially with the existence of open borders. It has been reported that 97% of the medicine in Iraq now comes from unknown origins especially with the absence of the regulatory authority and the fear of health inspectors of being assassinated if they report any incident of counterfeiting (Mason and Ali 2005).

Since the opening of the borders, there has been a wide spread of counterfeit and substandard pharmaceuticals in Iraq. Before the invasion of Iraq there were two authorized pharmaceutical manufacturers in the country, but after the war many unlicensed pharmaceutical manufacturers have spread which led to a lack of good manufacturing practice (GMP), and unlicensed drugs street vendors (Mason and Ali 2005).

1.3.4 In Lebanon, The Ministry of Health launched a public awareness campaign to fight the counterfeit trade in the country. In 2004, reports by Lebanon's parliamentary health committee estimated that as much as 35% of the drugs sold in the country are counterfeit. The health ministry indicated that the ranges of drugs that have been counterfeited include common painkillers such as panadol, antidepressant such as xanax, and the impotence drug, which is highly, counterfeited Viagra (Ghosn 2008).

Lebanon lacks any specific laws regarding counterfeit medicine, but the Health Ministry in collaboration with activists within the industry has launched a number of campaigns aimed at raising public awareness, including a high profile media campaign conducted in 2006 and a TV campaign launched last year (Hall 2009).

1.3.5 In Syria, is another neighboring country with Jordan the problem of counterfeit medicines is also a big concern for the authorities in Syria. It is estimated that 20% of the counterfeit medicine that is available in the country is an imitation of locally produced medicines, while 80% is counterfeit for imported medicines (Morei 2009).

1.4WHO Historical Involvement in Counterfeit Pharmaceuticals

Concern for quality of pharmaceuticals in international trade started since the establishment of the World Health Organisation (WHO) in 1948. In 1951, the (WHO) Executive Board adopted resolution EB7.R79, which asked for consideration of the advantage of a more unifying method for drug control worldwide (Martijn 2003).

The first appearance of counterfeit medicines in international trade was realised as a problem at the WHO Conference of Experts on Rational Drug Use in Nairobi, Kenya, in 1985 (WHO 2005).

Since then, public awareness of the problem of counterfeit drugs has gradually grown (WHO 2005). Both government authorities and manufacturers have engaged in different levels of efforts aimed at attacking the problem.

In 1988, the world health assembly adopted resolution WHA41.16 that aimed at initiating programs for the prevention and detection of the export, import and smuggling of counterfeit and substandard pharmaceuticals (WHO 2005).

In April 1992, WHO and the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), in Geneva, organised the first international gathering on counterfeit drugs.

In 1995, using financial support from the government of Japan, WHO launched a project on counterfeit drugs, to help member states in the assessment of the counterfeit problem by the development of measures to combat counterfeiting (WHO 1999).

Guidelines for developing measures to combat counterfeit drugs have been prepared within the framework of the world health organisation (WHO). Their purpose was to assist member states of WHO in efforts to prevent the infiltration of national drug distribution channels by counterfeit drugs.

These guidelines were aimed mainly at government, national drug regulatory authorities, national law enforcement agencies and the judiciary. It was hoped that they might also be useful to pharmaceutical industry, drug importers, distributors, relevant professional associations and consumers.

In the same year, WHO developed a program on drug counterfeiting where 30 experts from drug regulatory authorities, international non-government organisation (NGOs), and other involved institutions participated. The aim of such an activity was to have a forum whose main responsibility is to assess the status of the problem and possible solutions. It also aimed at the establishment of a network designed to strengthen the measures against counterfeiting and the development of a manual to assist governments in the implementation of these actions (WHO 1999).

In November 1997, an international workshop on drug counterfeiting was held. One of its recommendations was that WHO continues its role as an observer for the purpose of collecting and analysing reports and monitoring the situation in the member states.

In 2004, regulatory authorities of more than 60 countries met in Madrid for a two-day satellite conference on counterfeit medicines. This conference was organised by WHO in

collaboration with member states regulatory authorities. Strategies and international collaboration on combating counterfeit drugs was discussed (WHO 2006 a).

In recent years, some countries have participated in efforts to fight the counterfeiting of drugs through passing legislations that are more specific, strengthening existing legislations, and establishing agreements for cooperation.

For example, the regulatory authority in Nigeria (NAFDAC) has restricted imports from 30 foreign companies. Nigeria usually maintains inspectors in exporting countries to ensure that drugs exported to Nigeria meet the required standards.

Another example was when the ministry of public health In Peru launched information campaigns calling on Peruvian citizens to purchase medicines only at registered pharmacies (WHO 2006).

As a result, WHO started to receive reports related to counterfeit drugs from some of its member states on a voluntary basis. However, with all these activities the definitions of counterfeit medicine was not yet unified among delegates of different countries.

1.5 Definition of Counterfeit Drug

In reality, the reason that has aggravated the problem of counterfeiting is that each country defines counterfeit medicine differently, so what is considered counterfeit in one country might not be considered counterfeit in another. This fact indicates the necessity of having a global understanding of the counterfeit problem and a unified definition of what exactly constitutes a counterfeit in order to make a better understanding of the problem of counterfeiting.

There is no unified methodology of defining a counterfeit drug at a global level. The definition, which is usually used in practice, was based on the laws and regulations of different countries, which created a conceptual problem for parties who engage in the collection of data and the implementation of measures to combat counterfeit drugs.

Most available definitions have concentrated on the magnitude and characteristics of the counterfeit drug.

Appendix (B) shows different definitions for counterfeit drugs as defined in different countries, (WHO 2007 a).

In this thesis, the WHO definition of counterfeit pharmaceutical issued as an official definition. The Jordanian statement of counterfeit definition is also used.

The (WHO) and the International Federation of Pharmaceutical Manufacturers Association established in 1992 a working definition of counterfeit drugs, which is still in use by the WHO today.

Following is the WHO definition:

"As one which is deliberately and fraudulently mislabeled with respect to identity and / or source. Counterfeiting can apply to both branded and generic products, may include products with the correct ingredients or with wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging." (WHO 2007 a).

In Jordan, in the year 2008, new legislation was enacted to specifically define a counterfeit drug. It stated that the medicine is considered counterfeit when:

- The medicine is manufactured in an unauthorised place or manufactured by a manufacturer other than the original one or without written permission of it.

- The medicine does not contain an active ingredient or a different amount of active ingredient than stated in the original label.
- The medicine has a counterfeit trademark or a counterfeit label
- The medicine has a fraudulent country of origin either inside or outside packaging (Public health and pharmacy law 2008).

In all definitions, counterfeiting is realised when the drug does not have active ingredients or contains active ingredients less than the genuine ones. Usually counterfeiters reduce the amount of active ingredients to the minimum just to get positive results in the identification test.

A drug is also considered counterfeited if it contains harmful ingredients, or has active ingredients but manufactured by an unauthorised manufacturer. The rule is that, even if only the packaging is fake, these drugs remain dangerous because they were produced without following a proper quality control system, as manufacturing guides indicate the present work.

The WHO definition has three characteristics that the drug should have in order to be classified as counterfeit. These characteristics focus on the fact that a counterfeit is a forgery, a copy or imitation, is made without authority or right, and with an intention to deceive or defraud, by introducing the copy or imitated drug as the original or genuine one.

The definition of counterfeit used in Jordan conforms to the WHO definition, and in addition to that, it places a great emphasis on complying with trademark law, and intellectual property rights.

For the purpose of this research, the WHO definition of counterfeit drug is going to be used.

In discussing counterfeit drugs there are many terms used and can be sometimes considered as counterfeit or facilitate the movement of the counterfeit drugs and these terms are: substandard, diverted, parallel trade. Following are the definitions of these terms:

1.5.1Substandard Medicine: According to the WHO, substandard medicines are genuine drugs, which do not meet the quality specifications designed for them and are usually produced by legitimate manufacturers (Caudron *et al.* 2008).

The United Stated Pharmacopoeia defines substandard product as "*legally branded or generic products, but one that does not meet international standards for quality, purity, strength or packaging"* (Caudron *et al.* 2008).

Substandard medicines are often made without complying with good manufacturing practices (GMP), or do not conform to the pharmacopoeial standards set for them (U.S. Pharmacopoeia 2004).

Good Manufacturing Practices (GMP) are required standards set forth by the authorities in order to ensure that the products are always produced at the required quality levels. GMP are considered as general guidelines that should be followed during the engagement with pharmaceuticals starting from the raw materials, through the processing, packaging, labeling and finally when the final product reaches the consumers (WHO 2003 c).

Substandard pharmaceuticals normally contain less active ingredients than what the label claims.

Therefore, poor compliance with Good Manufacturing Practice (GMP) can lead to substandard drugs; this may be accidental, or because of insufficient resources, lack of specific expertise, or lack of appropriate manufacturing infrastructure (Caudron *et al.* 2008).

Substandard medicines can have serious public health consequences such as contamination, which can cause fatal toxicity, (Caudron *et al.* 2008). Lack of active ingredients can lead to ineffective treatment and prolonged illness or death. Finally, under dosing of active ingredient may have the additional risk of causing drug resistance.

1.5.2 Drug Diversion: This occurs when pharmaceutical products do not follow the proper distribution chain from the manufacturer to the patient. Instead, diverted pharmaceuticals pass through a complex series of transactions before being dispensed to the patient.

Drug diversion is considered a threat to the public because some of these drugs may have passed their expiration date, some may not be stored under proper conditions, or some may have false labels.

The problem with drug diversion is that it may facilitate the counterfeit medicine to enter the distribution chain and appear legitimate.

1.5.3 Parallel Trade occurs when products protected by patent, trademark or copyright are first distributed into one market then re-imported into a second market without the authorisation of the original manufacturer, the owner of the intellectual property rights (IPRs). The main motive for Parallel trade is usually to realise a high profit rate due to the different price levels (Arfwedson 2004).

This process of parallel trading includes repackaging and relabeling medicines, which may create opportunity for counterfeiters to enter their products into the distribution chain.

Those who support parallel trade maintain that parallel trade can lower prices, especially for consumers and government, who are looking for ways of reducing health expenditure.

As is the case in European Union countries, due to different national prices between European Member states, parallel trade occurs by purchasing medicine from countries with low prices, importing them into countries where pharmaceuticals were usually sold at higher price and thus making profit utilising the deferential of prices (Arfwedson 2004).

It has been found in many investigations in prior studies that the longer the chain of distribution the more chance of introducing counterfeit or substandard pharmaceuticals and this could have the affect of not knowing the source of the drugs in time of recalls (Catizone 2006).

1.6 Historical Development of Counterfeit Trade

The first appearance of counterfeit medicines was seen as a progression of substandard medication, which was usually produced by legitimate manufacturers but with insufficient, or without active ingredients.

This problem was further aggravated due to the advances of high technology, which made it possible for counterfeiters to imitate drugs in order to generate more profits.

In the past, the counterfeited pharmaceuticals that are being targeted are usually differing in type between developed and developing countries. In developed countries the counterfeiters targeted life style medications such as Viagra and hormones, but now they have expanded their business to include all types of medicine especially life saving ones, and the newer

brand names and the highly priced medications such as anti-cancer, and anti-HIV medicines (WHO 2003 a).

In the developing countries, counterfeiters also targeted generic drugs that are used in widespread diseases, life threatening diseases such as tuberculoses HIV/AIDS, higher priced medications such as anti-cancer, and growth hormones, and medical consumables such as gauze, and other medical appliances.

Counterfeit drugs were responsible for more than 100.000 deaths each year in South East Asia as a result of taking fake drugs (Stevens 2006). Half of the drugs sold in South East Asia for malaria are counterfeited and do not contain the required level of active ingredients; as a result, drug resistance to anti-malarials has been generated.

In general, with the spread of this phenomenon more and more medications are being targeted by the counterfeiters.

Counterfeiters have made use of improved quality of the packaging due to the use of high technology, which makes it hard for consumers and the law enforcement authorities to differentiate between legitimate and counterfeited medicines.

It is a well-known fact that, the presence of these counterfeited medications affects the credibility of health care system, which normally suffers when the counterfeit medicines get into the legitimate distribution channels.

There are many types of pharmaceutical counterfeit as categorized by World Health

Organisation:

1. Products without active ingredients.
2. Products with incorrect quantities of active ingredients.
3. Products with wrong ingredients.
4. Products with correct quantities of active ingredients but with fake packaging.
5. Products with high levels of impurities and contaminants (WHO 2007 a).

In 2002, the World Health Organisation estimated that as much as 5% of the medicine consumed in developed countries are counterfeit, compared to more than 10% in the developing countries. In 2006, it was reported that approximately 10% of the medicines consumed in developed countries were counterfeit, while 25% was reported to be counterfeit in developing countries. In some countries, the figure reaches more than 50% (WHO 2006 a).

The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) reported a 32% increase in the number of countries which are experiencing counterfeiting incidents from 67 countries in 2004 to 89 countries in 2005 (Wertheimer and Norris 2009).

It has been reported that the sales of counterfeit medicines globally is approximately between US$ 37 - 40 billion for 2005. The Center for Medicines in the Public Interest, in the United States, predicts that counterfeiting sales will become US$75 billion globally in 2010, an increase of more than 90% from 2005 (WHO 2006a).

Basically, all features of drugs were subjected to counterfeiting: active ingredients, dosage form, package inserts, packaging, manufacturer's name, batch number, expiry date and documentation relating to quality controls (German Pharma Health Fund 2004).

Despite the fact that this trade is expanding, authorities in different governments and pharmaceutical industries show reluctance to report cases of counterfeit fearing that the public loses confidence in medicine and might stop taking their medications, in addition to the fear that publicity might harm the sale of medicine and reputation of the industry. Despite the efficient reporting system WHO maintains, it received only 84 reports of counterfeit drugs between 1999 and 2002 (Cockburn *et al.* 2005).

1.7 Factors Affecting the Growth of Counterfeit Pharmaceuticals

The problem of counterfeit medicines is well recognised globally, in both developed and developing countries. An important factor that contributes to the spread of this trade is the lack of a clear definition for counterfeit product. Many countries have their own definition of what is considered counterfeit, which creates a problem in defining the term counterfeit product, therefore what is considered a counterfeit in one country might not be considered counterfeit in another. This indicates how significant it is to have a universal definition to be applied in all countries (Kelesidis *et al.* 2007).

It addition to the above major factor there are some other factors:

1- The financial gain acquired by counterfeiters, since these pharmaceuticals are produced without any manufacturing standards to comply with and away from any quality control systems. These are normally expensive due to the requirement for applying Good Manufacturing Practices (GMP) which are usually required from legitimate pharmaceutical manufacturers.

2- The high price of genuine drugs and insufficient medical health insurance, especially in developing countries, has led consumers to look for lower price medications that are possibly counterfeited. This explains the fact that poorer segments of societies are most affected by counterfeiting.

3- Weakness or absence of drug regulatory authorities or lack of drug legislation and appropriate enforcement.

4- The use of high technology to produce high quality packaging to replicate legitimate drugs making it hard to distinguish between the real and counterfeit medicine.

5- The non-traditional ways of buying drugs through the internet and mail delivery, especially in developed countries, which offer a huge opportunity for counterfeiters to sell their products.

6- Corruption in certain legal systems, especially in developing countries, where actions are not decisive when a counterfeit drug is discovered.

7- Government actions to encourage people to look for cheaper medicine because prices of legitimate drugs are higher due to higher levels of taxes and tariffs.

8- The pharmaceutical industry keeps the data of fake medicine secret for Security and fear that the publicity might harm the sales of their brand name drugs (Cockburn 2005).

9- Complex transactions involving many intermediaries such as having more than one wholesaler, which prolong supply chain system thus increasing the opportunity of counterfeiter's penetration.

The production of counterfeit drugs occurs in many countries but China and India are considered the main producers for these formulated drugs and the bulk active ingredients, which are used all over the world for the production of counterfeit drugs (Khan and Ghilzai 2007).

The counterfeit threat is considered as a problem because:

- The inability of traditional drug distribution channels to identify counterfeit.
- Non-traditional drug distribution systems such as (the internet and postage systems) are growing without proper regulation to avoid counterfeit drugs.
- Evidence is normally destroyed when the drug is ingested or injected, and if the patient does not get better, few people suspect that the drug is counterfeited.

1.8 The Use of Counterfeit Medicines can be Harmful in Many Ways:

1- The use of toxic chemicals causes injury or death, as in the case of using antifreeze, which resulted in 89 deaths in Haiti in 1995(WHO 2006a).

2- The use of insufficient amount of active ingredients prevents the medicine from being effective. Counterfeit medicine is responsible for increasing drug resistance among very dangerous infectious diseases such as: malaria, HIV/AIDS and tuberculosis (TB) because these medications contain incorrect active ingredients which causes some strains of bacteria and viruses to mutate, multiply and spread which results in serious illness and death as a result of improper treatment (Morris and Stevens 2006).

3- The use of counterfeit drugs could cause adverse effects, especially if they contain toxic materials, or pathogenic contaminants. Pathogens have been found in case of

counterfeited drugs where gentamicin eye drops was contaminated with gentamicin-resistant pseudomonas aeruginosa which led to severe eye infections (Newton *et.al* 2006a).

There are numerous cases of counterfeit medicine but the following are some examples:

- Paracetamol syrup prepared by using glycerol which was contaminated with diethylene glycol (a toxic chemical used as an anti-freeze) 89 people died in Haiti in 1995(WHO 2006 a).
- During the meningitis epidemic in Niger, vaccines were contaminated, 2500 people died after being vaccinated by contaminated vaccine (WHO 2006a).
- It is estimated that in 2001 in China alone, counterfeit drugs caused the death of 192,000 patients, and the Chinese government closed 1300 factories involved in the production of counterfeit drugs (Newton *et al.* 2006 b).
- WHO estimates that 200,000 of the one million malaria deaths a year would have been prevented if all the drugs were genuine (Clarck, 2008).

1.9 What has been done to address the Problem?

There have always been international efforts to combat the problem of counterfeit medicine. In 2005 the (WHO) established the "Rapid Alert System" (RAS) a mechanism serving as a rapid alert for member states and partner organisations who engage in combating counterfeit medicines in the Western Pacific Region .

When counterfeit medicine is detected in the region and reported through the RAS, relevant authorities are notified immediately and relevant actions are taken (Wertheimer and Norris 2009).

In 2006, The World Health Organisation (WHO) has created an International Medical Products Anti-Counterfeiting Task Force (IMPACT) to try to coordinate different efforts to control this illegal trade around the world. Their major concern is to increase the public awareness of counterfeit drugs and to encourage the consumers to report any suspected counterfeit products (Khan and Ghilzai 2007).

The United States Food and Drug Administration (FDA) also created an internal Task Force in order to control and prevent counterfeit drugs from reaching consumers.

In the United Kingdom the Medicines and Healthcare Products Regulatory Agency (MHRA) has established the Defective Medicines Report Center (DMRC) to receive and assess complaints and reports of suspected defects and coordinates necessary actions resulting from these reports. As a consequence of such a warning, drugs are to be withdrawn from the marketplace and an alert is issued. This alert is classified on a scale from one to four depending on the seriousness of the defect and its impact on public health. Class 1 is the most critical, such as serious mislabeling, microbial contamination or

incorrect ingredients, and requires immediate recall, and Class 4 is the least critical and advises caution in use of the drug (MHRA 2006).

The European Parliament and the Council of Europe are considering new regulations (Andrew2007).

Companies have created the pharmaceutical security institute (PSI) and developed global security strategies to ensure public safety and product integrity (IFPMA 2006).

Therefore, in order to address the problem of counterfeiting, many aspects of cooperation and coordination among different stakeholders are needed: law enforcement agencies, drug regulatory, customs and the pharmaceutical industry. Specifically some actions can be taken:

1- To increase level of awareness of health professionals and the public so that they are able to discover, evaluate and report any incident of counterfeit in a timely fashion.
2- To enhance governments and other groups working for social and health concerns capabilities to educate the general public by utilising information campaigns, advertisements, and any other means of mass communication.
3- To encourage patients to report any deficiency in improvement of their health status or any adverse reaction observed by them to their physicians or health workers immediately (Dahiya 2008).
4- To encourage pharmacists to exert maximum care when choosing their suppliers.
5- It should be required that, governments should find ways to reduce the tax burden on medicines so the prices of genuine drugs can become affordable which should curb the prevalence of counterfeiters.

6- To enhance regulation by creating judiciary systems that are highly informed of the complications of counterfeiting issues and their impact on public health.

1.9.1 Pharmaceutical Measures

In fact, the pharmaceutical industry has utilised many technologies to control this problem. The objective of using these technologies was to make counterfeiting more difficult and more expensive.

In an attempt to protect against the counterfeit trade, the pharmaceutical industry has been trying to implement many measures. One of them was the use of authentication technologies such as the use of invisible ink, chemical taggants, tamper-resistant packaging tape and chemical markers.

The use of holograms is of particular significance. Holograms are a unique pattern that could be obtained through the interaction of laser beams that is produced by the manufacturer. The ability of holograms to provide effective protection lies in the continuous innovation in inventing holographic techniques (Deisingh 2005).

Lancaster (2008) has this to say about the advantages of holograms:

" Holograms are widely used now in different formats such as holograms to protect branded bottled products against counterfeiting and holograms for blister packaging, and holographic induction cap seals, polyester-based tamper evident labels used to seal packages, holographic hot stamping foil where the hologram is fused to the host surface by heat and pressure. Advantages to the use of security holograms include the following: they are difficult to counterfeit, they are recognizable to the consumer, and they are relatively cheap. "

Despite all of that counterfeiters have manage to produce low quality holograms in a way to deceive the authorities and the patients. It has been reported that, all the techniques above were imitated by the counterfeiters in a very short period. It has been noticed that within six months from using these techniques the counterfeiters were able to imitate them.

Another one was the use of serial numbers ID known as serialization, which can be applied to product packaging. This method, also called traces and track technology, uses different technologies including barcodes and Radio Frequency Identification (RFID) tags.

Barcodes technology is an identification method that allows each pack to have a unique serial number, which can be traced to insure the authentication of the product as it moves through the distribution channel (Rudolf 2004).

Radio frequency Identification (RFID) method uses a radio frequency chip that stores all the critical data related to a product in the form of electronic product code (EPC) or (electronic pedigree) which document the movement of the containers of the drug through the supply chain. It involves radio frequency chips applied to all medicine and computerised readers to trace their movement (Kontnik 2006 a).

"Drug pedigree is the statement that identifies prior sales, purchase or trade of the drug including the date of the transaction and the names and addresses of all parties to the transaction." (Kontnik 2006 a)

Chips can be hidden in a place that cannot be seen, and then a chip reader can trace the information on the chip as the product moves through the distribution chain. (RFID) is considered an effective method as an electronic tracking technology, with a cost varying from a few pence to several pounds depending on specifications such as data capacity, range and read/write capability of the taggant.

There are some problems related to the use of this technique, particularly when used with biotech medicine. The problem arises when radio frequency waves are absorbed by the proteins in the product causing degradation, which compromises the safety and effectiveness of the product (Crooker 2009).

Another problem associated with the use of radio waves is that these waves can be absorbed by the liquids and reflected by metals that make up most biotech products. This could make reading the tags attached to biotech products more difficult.

Another point worth mentioning here is that this technique is costly since it needs special equipment and a secure tracking system throughout the distribution chain to validate the RFID tags.

All of these problems made the implementation of this technique inefficient until pharmaceutical companies invent solutions to overcome such problems before full and safe implementation (Kontnik 2006 b).

In conclusion, there is no simple solution to eliminate counterfeit medicines, and the problem cannot be solved individually. The problem has reached a global level and needs a global approach that is why it is very important to rely on strong regulation and punishments in order to control the trade of counterfeit products.

1.10 Intellectual Property and Counterfeiting

The relationship between Intellectual Property and counterfeit is that counterfeiting is only one aspect of a larger problem of IP right infringement. While it is true that an increasing awareness of the importance of IP is spreading worldwide, therefore IP protection has became an important element of international trade agreements and many trade issues were linked to such protections. Consequently, the problem of counterfeit drugs has been approached internationally through multilateral trade negotiations.

As a result, many countries, which have no anti IP regulations, were forced to develop regulations in order to avoid trade sanctions. Thus, many third world countries adopted legislation to guarantee IP laws and enforcement. But due to the severe lack of resources to enforce these laws, IP protections become laws without effective enforcement a situation that aggravates the problem rather than solving it. However, the fact remains that strong IP Rights and enforcement mechanisms are vital in the fight against counterfeit drugs.

The pharmaceutical industry depends on IP rights to help in the recovery of substantial amounts of investment in the creation and marketing of new drugs.

Therefore, it is important that, the acquisition and proper enforcement of IP rights should be maintained in order to support companies in their effort to protect themselves and their consumers from fake drugs.

To combat counterfeiting, trademarks and patent rights provide the most relevant IP protection.

Trademark laws are usually designed to protect against unauthorised use of a product's name or appearance in a way that is confusing due to similarity to a product that is used by

a legitimate producer. Therefore, counterfeiting occurs when a counterfeited drug appears to be manufactured by the authentic manufacturer even upon careful inspection.

Trademark owners can initiate a judicial claim against anyone who makes, sells or distributes counterfeit medicines that infringe their marks.

Patent laws provide protection against unauthorised manufacturing, use or sale of an authentic drug product or medical process.

In many countries around the world, IP violations can also be subjected to criminal prosecution in terms of fines or imprisonment. In many countries, IP rights can also be intersecting with customs laws, which create new mechanisms to fight counterfeiting (Falrbalrn *et al.* 2007).

In 1998, Jordan initiated a TRIPS implementation reform that aims at placing Jordan in compliance with the world trade organisation legislation.

TRIPS regulations (Agreement on Trade-Related Aspects of Intellectual Property Rights) included an agreement related to the law and policy of patent, copyrights, and trademark.

1.11 Statement of the Problem

This investigation focuses on evaluating the nature and magnitude of the counterfeit problem in Jordan, so that a reliable estimate of the presence of counterfeit drug in the Jordanian market in four life- saving medications can be obtained.

This statement of the problem is formulated in such a way that aims at specifically providing an answer to the following research question:

Does a counterfeit drug problem exist in Jordan? If it does exist, to what extent does it constitute a health problem?

1.12 Aims and Objectives of the Study

This investigation aims to obtain a reliable and unbiased estimate of the presence of counterfeit drugs in four life saving medications that are commonly used within the Jordanian market.

At this point it seems to be relevant to mention that, this study aimed at uncovering the status of counterfeit drug in Jordan, therefore it is not directing to any specific drug.

To reach this end, the researcher intended to collect samples of the following medicines and analyse them to identify their active components as well as the level of compliance to Good Manufacturing Practices (GMP).

The study examined the problem of counterfeit pharmaceuticals by considering all aspects of pharmaceutical compliance including labeling, content, distribution, quality and regulation.

1.13 Specific Research Objectives

Following are the specific objectives of this research:

1. To evaluate the current state of counterfeiting of sampled medicines.
2. To assess the current state of counterfeiting regulations in Jordan, and emphasize different approaches to fight this trade:
    a- To suggest total collaboration between responsible parties such as; Jordan Food and Drug Administration (JFDA), drug stores, the police and the customs, to combat the counterfeiting problem.
    b- To highlight efforts providing professional training for personnel of drug regulatory authorities, police, customs and judiciary on how to identify

counterfeit drugs, and the risk involved for the public by using counterfeit drug.

c- To ensure the adoption of strong anti- counterfeiting laws and regulations to fight counterfeit medications.

1.14 Essential Pharmaceuticals

It has been reported by the World Health Organisation (WHO) that in developing countries, counterfeit pharmaceuticals often involves essential drugs that are used for life threatening diseases such as the sample of pharmaceuticals in this study (Aka *e.al.* 2005). WHO has defined essential medicines as:

" those drugs that satisfy the health care needs of the majority of the population, they should therefore be available at all times in adequate amounts and in appropriate dosage forms, at a price the community can afford."(WHO 2007 a).

Each country has usually maintained its own list of essential medicines. This list constitutes the minimum level of medicines needed for basic health requirements for priority conditions based on estimated future requirements. The list is usually viewed as an important action, because it is considered as the basis of national drug policy and governments refer strictly to the WHO requirements when making decisions of such a type (WHO 2007 b).

In this study, the reason behind selecting these samples of life saving medications as samples for this study was that these pharmaceuticals have been targeted by counterfeiters in the past due to their high prices and high demand, which made these products attractive targets to counterfeiters, who benefit from the sale of large amounts of products in a short period of time. They are considered very popular due to their well-known brand names.

At the international level, the four pharmaceuticals were considered among the 200 best selling medications worldwide in the year 2008 (Humphreys 2010). Based on total sales in 2008, Lipitor was classified as the number one highest selling drug with sales amounting to $13,375 million while Plavix was ranked the second best selling medicine worldwide with total sales of $9,455 million in 2008. Co-Diovan was ranked six in the list with sales of $5,740 million, and Concor ranked 171 on the list with sales of $638 million in the same year.

At the local level, these four pharmaceuticals were identified as the four highest selling pharmaceuticals each within its group according to International Market Statistics (IMS), which is an international market surveying group operating in Jordan in the area of sales screening (IMS 2010).

Following are some basic information about the selected medicines:

- Lipitor (atorvastatin) belongs to a group of drugs known as statins. Statins include Zocor (simvastatin), Lescol (fluvastatin), and other pharmaceuticals as listed in table

(1-1) Statins reduce total cholesterol as well as LDL cholesterol in blood by preventing the production of cholesterol in the liver by blocking HMG- CoA reductase, the enzyme that produces cholesterol. LDL cholesterol is known as the "bad" cholesterol that is primarily responsible for the development of coronary artery disease. Therefore reducing LDL cholesterol levels stops progression and may even reverse coronary artery disease. Atorvastatin also reduces the concentration of triglycerides in the blood and raises the concentrations of HDL ("good") cholesterol (Medicine net. 2010).

Table (1.1): Statin Group Sales in Jordan (IMS 2010).

As shown in table 1-1 Lipitor was ranked number one selling drug in Jordan from the group of Statin pharmaceuticals. As shown, 980,000 units of Lipitor were sold in the year 2009 from the total sales of 3,699,000 units for all medicines in the group. This means that Lipitor market share was 25.2%.

It a well known fact that atorvastatin is rapidly absorbed after oral administration, with maximum plasma concentration of 1–2 hours. The absolute bioavailability of the drug is approximately 14%; however, the systemic availability for HMG-CoA reductase activity is approximately 30%. Administration of atorvastatin with food produces a 25% reduction

in rate of absorption and a 9% reduction in extent of absorption, although food does not affect the plasma LDL-C-lowering efficacy of atorvastatin. Evening dose administration is known to reduce the rate of absorption and extent of absorption by 30% each. However, time of administration does not affect the plasma LDL-C lowering efficacy of atorvastatin. Atorvastatin is highly protein bound (≥98%).

The most common adverse side effects are raised liver enzymes and muscle problems. (Appleby and Sternberg 2002).

- Plavix (clopidogrel) is an anti-platelet agent (thienopyridine class) which is used to prevent blood clots in the coronary artery, and used for the prevention of thrombosis after placement of intracoronary stent (Berger 2007).

Table (1.2): Thienopyridine Group Sales in Jordan (IMS 2010)

As shown in table 1-2 Plavix was ranked number one selling drug among its group in Jordan. 18,000 units of Plavix were sold in year 2009 out of 22,000 units sold from the same group. Plavix market share was 84.9% in the year 2009. After repeated 75-mg oral doses of clopidogrel (base), plasma concentrations of the parent compound, which has no platelet inhibiting effect, are very low and are generally below the quantification limit (0.000258 mg/L) beyond two hours after (Simon *et al.*2009).

Clopidogrel is rapidly absorbed after oral administration of repeated doses of 75 mg clopidogrel (base), The pharmacokinetics of the main circulating metabolite are linear (plasma concentrations increased in proportion to dose) in the dose range of 50 to 150 mg of clopidogrel. Absorption is at least 50% based on urinary excretion of clopidogrel-related metabolites. Certain serious side effects include skin irritations, respiratory difficulties, bloody stools and vomit, bloating of facial features, limbs and joints, exhaustion etc. (Simon *et al.* 2009)

- Co-Diovan is a drug that belongs to a class of medicines known as angiotensin II antagonists in combination (valsartan) with diuretics (hydrochlorothiazide). It is usually used to regulate blood pressure.

Table (1.3): Group of Angiotensin II Antagonists Sales in Jordan (IMS 2010)

As shown in table 1-3, Co-Diovan was ranked number one selling drug in Jordan among its group in the year of 2009. A total of 27000 units was sold out of 83000 unit sold for the whole group. Co-Diovan market share was 37.5% in the year 2009.Valsartan is rapidly absorbed after oral administration.

The mean absolute bioavailability of valsartan is 23% (range: 23±7%). The plasma concentrations in men and women were similar. If taken during a meal, the area under the plasma-concentration curve (AUC) for valsartan is reduced by 48% and the C max by 59%. However, from 8 hours after ingestion of valsartan in the fasting state or with a meal, the plasma concentration is comparable. The reduction of the therapeutic effect is so that valsartan can be taken independently of meals.

On the other hand hydrochlorothiazide is rapidly absorbed after oral administration (t max about 2 hours). The absolute bioavailability of hydrochlorothiazide after oral administration is 60-80%.

More than 95% of the amount absorbed is excreted via the kidneys, in unchanged form.

The most common side effects are: headache, dizziness, sensitivity to sun light and bright artificial light. (Briggs and Nageotte 2001).

- Concor (Bisoprolol) is a drug belonging to the group called beta-blockers. This group is used in cardiovascular diseases such as hypertension. It usually reduces blood pressure by blocking off the cardiac beta-receptors. It is also used to treat coronary heart disease, arrhythmias, and ischemic heart diseases (Medicine net. 2010).

Table (1.4): Group of Beta Blockers Sales in Jordan (IMS 2010)

As shown in table 1-4 Concor was ranked number one selling drug among its group of (Beta Blocking Agents). 80,000 units of Concor were sold in 2009 out of 251,000 units sold of the whole group. Concor market share was 27.6% in the year 2009.

Bisoprolol has both lipid and water-soluble properties making it a prime candidate over other β-blockers and even over other β1-blockers, being water soluble it will have decreased incidence of central nervous system side effects (inability to diffuse into brain) compared to purely lipophilic compounds. Bisoprolol has an approximate half-life of 10-12 hours and when ingested has nearly complete absorption into the blood stream. The high

absorption is indicative of high bioavailability (approx. 90%). When being eliminated, the body evenly distributes it (50-50) between kidney excretion and liver biotransformation (then excreted). These factors make it a convenient once/day dosage when it is being administered.

Beta-blockers can precipitate asthma and this effect can be dangerous. Beta-blockers should be avoided in patients with a history of asthma or bronchospasm.

Following are the four medicines used in the analysis are:

- Co-Diovan (160/12.5) tablets.
- Concor (5mg) tablets.
- Lipitor (20 mg) tablets.
- Plavix (75mg) tablets.

CHAPTER TWO

REVIEW OF PREVIOUS COUNTERFEIT PHARMACEUTICALS SURVEYS

Chapter Two

Review of Previous Counterfeit Pharmaceuticals Surveys

In this section of the research, previous studies on counterfeit pharmaceuticals will be surveyed in order to provide solid theoretical background about this research problem.

The trade in counterfeit drugs is responsible for increasing drug-resistance especially for infectious diseases, such as malaria (Bate *et al*. 2008).Counterfeit medicines also have a negative impact on public perceptions of the effectiveness of pharmaceuticals.

Several studies were examined and indicated that the developing countries and the poorer countries are most affected by the counterfeit problem

In discussing counterfeit medicine, researchers usually used the term substandard medicine to refer to genuine medicines that are produced by legitimate manufacturers and which do not meet the quality specifications that the producer says they meet. Normally they contain active ingredient at doses less than the label claims (Caudron *et al.* 2008).

The most common source for substandard medicines is batches of a drug that fail one or more tests due to some manufacturing problem. Normally, they should have been destroyed but instead they get in some way into the legitimate distribution channel and consequently get into the market.

Another source is improper storage at high humidity or high temperature, which might affect the active ingredient in the drug, and could cause microbial contamination (Morris and Stevens, 2006).

Studies have indicated that 14 million people die every year of infectious diseases, 90% of them from the developing countries (Newton *et al.* 2006 b).

To test for counterfeit presence previous studies have utilised a number of testing methods such as a simple die test, thin layer chromatography (TLC), high performance liquid chromatography with UV detection (HPLC -UV), high performance liquid chromatography with diode array detection (HPLC-DAD), near infrared spectroscopy (NIR), disintegration tests, and dissolution tests.

Following are the previous studies, which have been used in this research.

2.1 Anti-malarials Pharmaceuticals

Malaria is usually caused by a parasite called plasmodium falciparum. Malaria remains globally the most important parasitic disease, with approximately one million deaths caused by Malaria each year (Tipke *et al*. 2008). Anti-malarial pharmaceuticals are among the most widely consumed drugs in tropical countries that have been particularly targeted by counterfeiters (Onwujekwe 2009).

This has created a high demand for anti-malarial medications consequently; this may explain why counterfeiters targeted anti-malaria pharmaceuticals.

2.1.1 Anti-malarials Pharmaceuticals in Africa

The level of the presence of counterfeits and sub-standard pharmaceuticals in African markets is considered a serious problem that causes many deaths each year. It is known that malaria is a major cause of morbidity and deaths worldwide. The most deadly form of the malaria parasite is known as Plasmodium falciparum, which is prevalent primarily in sub-Saharan Africa (SSA) (Amin and Kokwaro 2007).

In tropical countries in Africa, pregnant women and young children under 5 years of age account for 90% of victims (WHO 2003 b).

Because of the fact that Africa suffers from a high incidence of malaria and so there is a great demand for these medications across the continent, this has created more incentives for the counterfeiting trade.

The following studies were conducted on anti-malarial medications to evaluate the quality of the medication used.

1- In a study conducted in South East Nigeria to evaluate the quality of anti-malarials in the country (Onwujekwe *et al.* 2009) researchers have collected 225 samples of anti-malarials which include artesunate, dihydroartemisinin , sulphadoxine- pyrimethamine (SP), quinine and chloroquine, this study was conducted in six towns (three urban and three rural) in Anambra state, south-east Nigeria. The samples were collected from randomly selected providers. The sample size was determined based on the range of providers and feasibility and was selected from a broader study of the nature of malaria treatment provision. In the broader study, 50 providers (public and private) in each urban and 25 in each rural area were selected, thus total sample size was 225 providers. The quality of drugs was evaluated through the purchase of anti-malarial drugs from a random sample of 20% of the 225 selected providers. They were spread out across the different levels of providers, but all existing public providers in each study area were included in the study.

The providers were divided into low-level providers and high/medium level providers. The low-level providers included patent medicine dealers, mixed goods shops and maternity.

The quality of these samples were evaluated by performing dissolution profiles using the United States Pharmacopoeial specifications for the monograms and high performance liquid chromatography (HPLC) to detect the quantity of the active ingredients in the samples.

Findings for HPLC analysis showed that 60 or 37% of the anti-malarials did not meet the (USP) specifications regarding the amount of active ingredients. Some of the drugs did not contain any active ingredient at all while others have active ingredient but with less quantity than was required. Results of dissolution tests revealed that 46% of the quinine and 39% of sulphadoxine -pyrimethamine (SP) formulations did not meet the tolerance limits that were required in the USP monograms.

Findings indicated that 78% of the samples that did not meet the (USP) tolerance limits were found in private facilities especially low-level health care providers. These private health care providers usually work in health care facilities that have many years of formal training but with no formal education and 94.5% of those providers are licensed. The researchers have concluded that there was a high existence of poor quality drugs in the country.

Findings have clearly indicated that there was a high prevalence of many substandard anti-malarial drugs in the study area.

The strength of this study was the large sample size and suitable methodology, which included the use of the powerful testing method of USP. The random sampling technique and the multi-level classification of the samples can also be considered as major strengths of the study.

2- Bate *et al. (*2008)collected 210 samples of mefloquine, artemether, amodiaquine, artesunate, dihydroartemisinin, and artemether-lumefantrine fixed-dose combinations from private pharmacies in urban and semi-urban areas in the major cities in six African countries.

The quality of these samples was chemically tested by performing thin-layer chromatography (TLC) and dissolution testing.

The Global Pharma Health Fund Minilab was used to run semi-quantitative thin-layer chromatography (TLC) and dissolution tests on each sample to determine the presence and relative concentration of active ingredients. Each test was done twice. The Minilab protocols award products a "pass" if they have 80% or more of the labeled active ingredients. For fixed-dose combinations and SP, "pass" was awarded only if both active ingredients met this standard.

Findings indicated that 35% of the samples analysed failed either TLC or dissolution or both tests. Researchers have identified the existence of artemisinin mono therapy, which is rejected by the world health organisation (WHO) and considered as substandard treatment even when its dosage is correct. The researchers found that 33% of the samples were artemisinin mono therapy, and 42% of them failed either TLC or dissolution tests.

Again, findings confirmed the presence of substandard and clinically inappropriate medicines in the country.

This study followed a precise research protocol, which has generated reliable results. The sampling procedures were conducted in a way that guarantees good representation of different geographic areas.

3- In Sudan, (Alfadl *et al.* 2006) collected 50 samples of the most used anti-malarial drugs such as; chloroquine, quinine, artemether and mefloquine in different dosage forms; tablets, syrup, suspension and injections.

Six states in northern, eastern, western and central Sudan were chosen for sample collection to represent all Sudanese markets.

The sampling procedures were designed in a way to determine whether these procedures were adversely affected by transport and storage conditions.

The quality of these samples was physically and chemically assessed. Chemical analysis was performed to determine the content of the active ingredients. Results indicated that 84% suffered physical failures especially for injections due to a change of colour were observed, 8% failed due to low content of the active ingredients in chloroquine tablets and 8% failed due to low dissolution rate for the same drug.

The researchers concluded that the physical failure might be due to transport and storage conditions. They concluded that the problem of substandard anti-malarial drug products is actually circulating in the Sudanese market.

Non-suitable distribution mechanisms as well as non-suitable storage conditions and non-compliance with good manufacturing practice (GMP) guidelines by manufacturers in production also seemed to have contributed to these results.

One major strength of this study was the countrywide coverage (all parts of Sudan were included in the sampling selection) which had made comparative evaluation possible using standard testing methods thus yielding reliable results.

2.1.2 Anti-malarials Pharmaceuticals in Southeast Asia

The problem of counterfeit and substandard drugs is a major concern in Southeast Asia. Malaria has become resistant to most of the available anti-malarial medications. Resistance develops from the exposure of the human malaria parasite to a non- therapeutic concentration of an anti-malarial drug.

The following studies were conducted in Southeast Asia to evaluate the quality of anti-malaria medications in the country:

1- In Cambodia, a study of 451 drug samples was conducted (Lon *et al*. 2006). Samples included mefloquine hydrochloride, tetracycline tablets/ capsules, dihyro artemisinin (DHA) tablets and artemether tablets.

The national and regional project teams were trained in the sampling method,

good laboratory practices and basic drug testing techniques, including physical and visual inspections, simple disintegration, thin layer chromatography (TLC), data documentation

and reporting. Three rounds were conducted in different areas of the provinces. The first round was conducted in April 2003. The drug outlets in a capital town of each province were selected using a pre-defined sampling protocol. The second and third rounds covered other drug outlets in the different districts in July and December 2003.

A sample from each lot of anti-malarial drugs was purchased. Samples were then subjected to testing procedures. The first level was basic testing performed at the sites using testing methods and procedures described in the Global Pharma Health Fund Minilab kit. The third level of testing was focusing on confirmation of selected samples at designated reference labs.

The quality of these samples was chemically assessed by simple disintegration and thin layer chromatography (TLC).

Results indicated that, 71.8% of the 85 quinine samples failed, 19.8% of the 81 artesunate samples failed, 7.7% of the 39 mefloquine samples failed, 8.5% of the 94 chloroquine samples failed and 26.6% of the 128 tetracycline failed.

Some of the failed samples were due to lack of active ingredients from the required amount. Some of them have no information related to the manufacturer or the origin of the product while some have fake holograms.

The researchers concluded that there is evidence of counterfeit and substandard anti-malaria drugs in Cambodia. Results of this study seemed to confirm that counterfeit and substandard pharmaceuticals are circulating in the country.

The major strength of this study was the training sessions held for the research team personnel prior to the beginning of the research process. This method contributed to reaching significant reliable results.

2- A study was conducted after the death of a 23-year old man from Burma who died after taking the drug artesunate, which is normally very effective for malaria treatment (Newton *et al.* 2006 b). This case was investigated by a team of experts from Oxford University. The analysis was conducted by applying mass spectrometry to identify the active ingredients in the medicine and high performance liquid chromatography to determine the amount of the active ingredients in the medicine. Results indicated that, the main active ingredient was paracetamol (acetaminophen), which can temporarily lower malarial fever but does not kill the parasite. Only 20% of the active ingredient was present, 10 mg per tablet instead of 50 mg, which was stated on the label. In the

same study the researchers reported that the percentage of over-the-counter counterfeit pills that contain no artesunate have increased from 38% to 52% in Southeast Asia from 1999 through 2004.

Results of the study on this case have confirmed the danger of the existence of substandard or fake anti-malarial medications.

2.1.3 Anti-malarials Pharmaceuticals in Yemen

In Yemen, Malaria has always been viewed as a major public health problem. It is believed that treatment failure associated with drug resistance may also be due to poor pharmaceutical quality.

Abdo-Rabbo, Bassili and Atta (2005) have conducted a study with the objective of assessing the quality of anti-malarial drugs that are commonly used in the country, particularly Chloroquine Phosphate tablets (CQT), Chloroquine Phosphate syrup (CQS) and Sulfadoxine/ Pyrimethamine tablets (SPT). Researchers included four samples from each anti-malarial product from various levels of the distribution chain.

Four samples from each anti-malarial product were collected from each of the various levels of the distribution chain. One sample was kept with the research team. Two were tested at Sana'a and Aden Drug Quality Control Laboratories. The fourth was sent to the Centre for Quality Assurance of Medicines in Potchefstroom, South Africa, for analysis. Quality indicators measured were the content of the active ingredient and dissolution rate (for tablets only) in comparison to standard specifications for these products in the relevant pharmacopoeia.

The analysis of the samples was conducted using a high pressure liquid chromatography (HPLC) method, and dissolution testing was performed for tablets only. Results indicated that the content of the active ingredients for (CQT) fails the standard limit significantly by 20%, and some dissolution failure for the same drug. As for (SPT) active ingredient was found within the standard limits content but showed a high failure rate in the dissolution testing.

Results seemed to indicate that the failure detected in this study could be considered as a serious problem. This problem indicates that there is sub-standard anti-malarial products circulating within the drug distribution chains in Yemen, and the dissolution failure indicates a non-compliance with good manufacturing practice guidelines by the manufacturer in the production of anti-malarial pharmaceuticals.

Researchers recommended that, an intervention plan should be developed and implemented immediately in Yemen. This may involve establishing quality surveillance systems within drug regulatory authorities in the country. The objective of these systems to provide the required support to manufacturers to improve Good Manufacturing Practice (GMP) compliance and promote effective management of drug supply.

The lessons that should be drawn from this study could be significant in helping Yemen to fight counterfeit problem in the country.

2.2 Antibiotics Pharmaceuticals

There is growing global concern regarding counterfeit antibiotics medications. In particular, counterfeit antibiotic drugs are increasingly viewed as a major threat to public health with many serious consequences for patients in terms of increased mortality and morbidity and drug resistance.

Recent research has indicted that, all types of pharmaceutical products have been involved, particularly antibiotics and anti parasitic agents, are the most counterfeited products in developing countries.

2.2.1 Antibiotics Pharmaceuticals in Pakistan

Pakistan ranked 13th in world for the practice of producing and selling counterfeit pharmaceuticals. Obaid (2009) conducted a study to evaluate the quality of ceftriaxone sodium which is widely used as a third generation cephalosporin (antibiotic) in the country the researcher collected 96 random samples of different strength injections (250, 500 and 1000 mg) from different pharmacies, medical stores, and hospitals in the country. The quality of these samples was evaluated by utilising the United States' pharmacopoeia (USP 2006) method with 90-115% limits to perform high performance liquid chromatography (HPLC) to evaluate the content of the active ingredients.

Findings indicate that 15.62% of the samples were out of pharmacopoeial specifications (90-115%). It showed that none of the samples was counterfeit but 7.29% of them were found to be above the limits ranging from 116 to133%, and 7.29% of them were below the lower limit ranging from 55 to 89% of the active ingredients.

The researcher concluded that there are ceftriaxone sodium injections in the country outside the pharmacopoeial specifications and there are manufacturers that do not comply with good manufacturing practices.

2.3 Anti- Parasitic Pharmaceuticals

Again the problem of counterfeit pharmaceuticals seem to influence all parts of the world even those very well protected health systems such as the Japanese health system.

2.3.1 Anti-Parasitic Pharmaceuticals in Japan

In Japan a pilot study was conducted (Aka *et al.* 2005), to assess the quality of theanti-parasitics, Albendazole and Mebendazole, in the country. Researchers selected these medications due to high demand for the use on worm infections which was widely used in Japan since there is worm infection prevalence in the country. To carry out their study, researchers have collected 44 samples of these medicines (15 Albendazole and 29 Mebendazole).

These samples were collected from 22 street vendors, in four cities in Japan. The testing of these samples included physical appearance and chemical testing which was performed by using thin layer chromatography (TLC) and high performance liquid chromatography (HPLC). The findings have confirmed the existence of the counterfeit medicine, where 9 out of 44 (20%) of the samples were found to be counterfeited. Results also showed that one sample of Albendazole was not produced by the labeled manufacturer and another sample was deliberately similar to a genuine one showing the same features but not the same amount of the active ingredient.

One sample of Mebendazole did not have any spot on the TLC plate, which means there is no active ingredient in the drug and that was confirmed after HPLC analysis was performed on the same sample. Three samples had incorrect registration numbers and their manufacturers were unknown; two samples had fake names and addresses, and one sample had an unregistered market name.

The results of this study seem to confirm the fact that counterfeiters can penetrate any health system regardless of how strong and protected it is.

The sampling procedures utilised in this study seemed to be suitable but the sample size was somewhat small in comparison with the size of the Japanese market.

2.4 Stimulant Pharmaceuticals

Amphetamine, the first manufactured stimulant, as well as fenethylline hydrochloride. Fenethylline hydrochloride (captagon) has been an extensively abused drug in many parts of the world. Due to their high degree of abuse and tendency to induce psychological dependence, their use is usually restricted to a few clinical conditions.

2.4.1 Stimulants in Saudi Arabia

In Saudi Arabia (Al-Hussaini 1996), a study was conducted to analyse the characteristics of captagon tablets, which has Fenethylline as the active ingredient. A total number of 900 batches of captagon tablets seized by drug controlling authorities were used as samples for the study. Each sample contains between 10 and 50 tablets, 10 tablets from each batch were used for the analysis. The samples were tested for their physical appearance such as (colour, hardness, diameter and markings) and their chemical characteristics. Physical

appearance indicated that all the seized tablets were narrower in diameter and thicker than the genuine captagon tablets. Also, the seized tablets were found to have two different colours (white and cream). The white group colour when analysed chemically were found to contained fenethylline with caffeine and /or quinine. While the other group, instead of having fenethylline, had a different compound. The chemical analysis was performed by thin-layer chromatography (TLC), it was noticed that some of the suspected captagon seized during 1990-1993 were found to contain pure paracetamol mixed with ephedrine in 10% of the samples while 13% of the samples contained amphetamine and ephedrine and some of the samples did not contain any compound but they appeared to be similar to the genuine tablets. The researcher concluded that the majority of the samples lack the active ingredient (fenethylline) which is the major active ingredient and instead other ingredients are replaced.

Researchers have also noticed that the trade of this drug continues, probably from the same source, and the composition of the tablets depends on the availability of the active ingredients during the time of manufacture.

This study seemed to be very significant in Saudi Arabia because it shed light on the counterfeit problem, which should facilitate policy-making measures to fight against this problem in this rich country.

2.5 Previous Studies in Jordan

Two previous studies indicated that there was a problem with counterfeit anti-biotic and stimulants in Jordan.

2.5.1 Previous Study on Antibiotics

In an attempt to evaluate the quality of antibiotics in developing countries, (Kyriacos *et al.*2008) collected samples of amoxicillin in different formulations produced locally and comparable sample from imported drugs.

The countries included in the study sample were Lebanon, Jordan, Egypt and Saudi Arabia. One hundred and eleven samples of amoxicillin capsules and suspensions from different pharmacies were collected and analysed using chromatographic methods to determine their content of the active ingredients.

Findings indicated that 56% of amoxicillin capsules did not meet the United States pharmacopoeia (USP) requirements, 8% of the samples of suspensions did not meet the pharmacopoeial limits, while the entire European brands met the pharmacopoeial limits except in one sample.

Researchers concluded that there were substandard medicines in the market of the tested countries. The existence of substandard medicine especially for antibiotics might cause treatment failure and produce drug resistance.

This particular study has confirmed the existence of substandard antibiotics in many middle-eastern countries among them was Jordan.

One major weakness however, was the small sample size, which was only 111 units of the medicines, which were collected from four countries.

2.5.2Previous Studies on Stimulants

Another study was conducted on a stimulant drug called Captagon, which has Fenethylline as the active ingredient (Albdalla 2005). This drug is known to be abused especially by young people and has been controlled since 1988 by The Drug Control Department of Public Security Directorate. One hundred twenty-four batches were seized by drug authorities and analysed to identify the composition of the drug. The findings of the study indicated that the majority of the samples lack the active ingredient (Fenethylline) which had been replaced by other ingredients such as caffeine, amphetamine and several other ingredients found in the drug. These ingredients were capable of inducing the same action as the genuine active ingredient.

These studies have contributed to the Jordanian government's extensive measures to deal with counterfeiting of pharmaceuticals. These measures included increasing penalties and other actions related to the importation and analysis of pharmaceuticals.

Therefore, the investigation of the impact of these measures made this research important to assess the effectiveness of such measures.

CHAPTER THREE

SAMPLING METHODOLOGY

Chapter Three

3. Sampling Methodology

This study includes testing four types of life saving medications manufactured by leading pharmaceutical manufacturers used in Jordan, which have been usually targeted in the past by counterfeiters due to their relative high prices.

In 2008, there were 1720 Pharmacies; pharmacies were selected as a sample for this study. The sampling was conducted in three stages.

The researcher collected samples of these medications from 33 community pharmacies in different districts of Amman for the first stage. Table (3.1) shows the number of districts and the number of selected pharmacies in each district.

The medicine found to be most counterfeited was planned to be included as a sample in the subsequent stage.

Collected samples were labeled , coded and information posted for each drug such as name of the sample, strength of the dosage form, location of the sample, the date of manufacture, the date of expiry, the batch number, the date of purchase and the name of the source.

To determine the genuine medicine from the counterfeited one, the physical appearance and the chemical were used as quality indicators in the analysis.

Tests included the use of Pharmacopoeial methods of high performance liquid chromatography (HPLC) for each medicine in the sample except for Lipitor, which was tested using dissolution test in addition to HPLC.

In order to have a clear idea about the medicines this study is going to test, a pilot study was conducted. Ten pharmacies were selected from the five areas of Amman and four

medications from each pharmacy were bought and subjected to lab analysis. These samples were coded and information about each medicine were posted, such as: name of the sample, strength of the dosage form, location of the sample, the date of manufacture, the date of expiry, the batch number, the date of purchase and the name of the pharmacy were documented.

3.1 Sample Collection

The sampled medicines are Lipitor (atorvastatin-calcium) a cholesterol lowering drug, Concor (bisoprolol fumarate) for hypertension, Co-Diovan (valsartan, hydrochlorothiazide) which is used to regulate blood pressure and Plavix (clopidogrel) a drug taken to prevent blood clots.

Sample collection included two types of medicines as follows:

1- Collecting samples of confiscated counterfeit medicines from official channels. Jordan Food and Drug Administration (JFDA) was the source of theses samples which usually obtains all confiscated products from customs authorities. This process was conducted in order to validate the testing procedures and ensure that the chemical analysis as well as the physical testing can distinguish between genuine and counterfeited pharmaceuticals.

2- Collecting samples of the four medicines circulating in the market. This process was done through two stages:

3.1.1 Stage One

Stage one includes the process of selecting thirty three pharmacies from the Amman area the capital of Jordan which represent 3.1% of total pharmacies in Amman (1063) and 1.9% of total number of pharmacies (1720) in Jordan. Four selected drugs from these pharmacies were bought and included in the lab analysis. Results of this process should determine the most common counterfeited drug from the four chosen drugs. The counterfeited drugs, if available was planned to be used for the next stage. This process provided the researcher with an opportunity to evaluate the magnitude of the counterfeit problem in the four different drugs and to identify if the problem is located in certain specific pharmacies.

For the sampling purposes, Amman the capital of Jordan which contains 1063pharmacies, was divided into five areas (north, east, south, west and the center of the city) in order to make the sampling procedures more accurate, and more representative as shown in Table (3.1).

Table (3.1) shows the different districts of Amman and number of pharmacies in each of them used in the analysis**.**

Table (3.1): Amman Districts and Number of Pharmacies

District	No. of Pharmacies	No. of Sampled Pharmacies	% of Total
East Amman	156	5	14.1%
West Amman	297	9	27.8%
North Amman	162	5	15.2%
South Amman	157	5	14.8%
City Center	293	9	27.6%
Total	1065	33	99.5%

The total number of sampled pharmacies were selected from each district and used in the analysis**.**

The first seventeen pharmacies were selected randomly from different areas in Amman, while the other sixteen pharmacies were selected from poor areas and pharmacies known to have high probability of engaging in counterfeit medicine trade, based on the JFDA experience.

3.1.2 Stage Two

Based on the study results after finishing the analysis, the most commonly counterfeited drug would be purchased from an additional 40 pharmacies for the investigation of stage two.

Figure (3.1): Map showing the three major populated cities (marked with red)

These samples should be chosen from the three largest cities in Jordan as shown in figure (3.1), The total number of pharmacies in Amman, Zarka, Irbid were 1063, 278 , 205 respectively. This will make the total sample to be 73 pharmacies out of the 1546 in the three cities (i.e. 4.7%) and 4.3% from1720 in whole of Jordan.

Consequently, a clear idea of the national distribution of the counterfeit problem should be gained.

CHAPTER FOUR

ANALYTICAL METHODOLOGY

Chapter Four

4. Analytical Methodology

This chapter presents the lab testing. The researcher would like to say that this study was not directed to any specific drug, but instead it aimed at the determination of whether counterfeit products do exist in the country or not.

This research has been conducted through two phases:

***Phase One*:** this phase describes the physical as well as chemical analyses of samples of the four pharmaceuticals obtained from Amman area.

4.1 Laboratory Chemical Testing

Quantitative testing was performed using high performance liquid chromatography. This method has the ability to accurately quantify the active ingredients present in the pharmaceutical preparations.

High performance liquid chromatography is a testing method used frequently to separate, identify and quantify the compounds. It consists of a stationary phase (column) and a mobile phase, which moves through the column, and a pump provides high pressure to move the mobile phase.

The major advantage of HPLC is that it is a sensitive, accurate and precise method of analysis. It allows a complex analysis to be done in a defined period of time and can accomplish the baseline resolution of components (Ho and Lin 1996).

HPLC is considered widely as a stability indicating method which selectively separates each active ingredient from its degradation products and in addition separates it from its process impurities and formulation excipients (Ho and Lin 1996).

Therefore, this testing method has a qualitative as well as quantitative nature. It also has the ability to detect the related impurities in the product. The process was performed according to pharmacopoeial specifications.

4.2 Drug References and Reagents

The Jordanian Pharmaceutical Manufacturing Co. (JPM) sponsored all chemicals used in the lab testing.

The following drug references were used:

- Bisoprolol Fumarate obtained from Moehs /Barchelona, assay 100.55%, water content 0.12%.
- Atorvastatin Calcium obtained from Biocon/ India, assay 98.5%, water content 4.0%.
- Clopidogrel Bisulphate obtained from Indu-swift/India, assay 98.0%, water content 3%.
- Related Impurities for Plavix and Co-Divan were USP references.
- Valsartan obtained from Ranbaxy Lab /India, assay 98.15%, water content 0.94%.
- Hydrochlorothiazide obtained from Shilton/India, assay 100.3%, water content 0.08%.

The following excipients and reagents were used:

- Tannic Acid obtained from Merck/ Germany.
- Methyl Alcohol for HPLC obtained from Acros organics /New Jersey, USA.
- Acetonitrile obtained from Merck /Germany.
- Potassium Dihydrogen phosphate (KH_2PO_4), obtained from Merck /Germany
- Phosphoric Acid 85% reagent grade obtained from (GFS) chemicals/ Germany.
- Acetic Acid obtained from Merck/ Germany.

- Ammonia obtained from Merck/ Germany.
- Sodium Hydroxide pellets obtained from Acros Organics/ New Jersey (USA).

4.3 Profiles of medications used in the analysis

Table (4.1) summarises some basic characteristics of the selected medicines in terms of active ingredients, dosage forms, strength, and number of samples.

Table (4.1): Active Ingredient(s), Dosage Forms, Strengths and Number of Samples Tested.

Trade Name	Active Ingredient(s)	Dosage Form	Strength	Number of Samples
Co-Diovan	Valsartan & Hydrochlorothiazide	tablets	160/12.5mg.	33
Plavix	Clopidogrel Bisulphate	tablets	75mg.	33
Concor	Bisopropolol Fumarate	tablets	5mg.	73
Lipitor	Atorvastatin	tablets	20mg.	33

Method of Analysis

All chemical tests for the study samples in this thesis have been done using high performance liquid chromatography for assay and related impurities. This method was adopted from the United States Pharmacopoeia (USP).

The United States pharmacopoeia (USP) is a collection of quality specifications for pharmaceutical substances and dosage forms together with general methods of analysis.

A monograph includes the name of the ingredient, the definition, packaging, storage, labeling requirements, and the specifications that the product must maintain in order to be ready for administration to patients.

The detailed specifications determined by pharmacopoeia are to be implemented to ensure the quality of pharmaceuticals which affect the safety and effectiveness of the drug. These specifications are usually enforced by authority in the country of manufacture using pharmacopoeial standards to ensure compliance (US Pharmacopoeia 2010).

4.3.1 Co-Diovan Analysis

Following are detailed description of Co-Diovan (160/12.5) analysis.

Co-Diovan has two active ingredients which are valsartan and hydrochlorothiazide.

1- (C_{24} H_{29} N_5 O_3). The chemical structure is shown in Figure (4.1) (Marks 2007).

Figure (4.1): Chemical Structure of Valsartan

2- ($C_7H_8ClN_3O_4S_2$). The chemical structure is shown in Figure (4.2) Beermann, Groschinsky-Grind and Rosen (1976).

Figure (4.2): Chemical Structure of Hydrochlorothiazide

Indications: Treatment of blood pressure (hypertension).

Dosage**:** One tablet daily.

The price: JD 31.75(£2**7.**10) per pack which contains 28 film-coated tablets.

Manufacturer: Novartis pharma (Switzerland)

In this research Co-Diovan was subjected to physical as well as chemical analyses. Physical testing conducted by visual inspection of the package.

Method of Analysis

Co-Diovan was chemically tested using high performance liquid chromatography for assay and related impurities. This method was adopted from the United States Pharmacopoeia (USP) verified in terms of linearity. Verification process indicated that this method is linear in the determination of valsartan and hydrochlorothiazide in Co-Diovan tablets. The linearity range for valsartan was between 10.002-30.006 mg/100ml, and linearity range for Hydrochlorothiazide was 0.798-2.394 mg/100ml.

The mobile phase consists of two solutions:

1. Solution A- a filtered and degassed mixture of water, acetonitrile, and trifluoroacetic acid (90: 10: 0.1) was prepared.
2. Solution B- a filtered and degassed mixture of acetonitrile, water, and trifluoroacetic acid (90: 10: 0.1) was prepared.

Standard and Sample Preparation for Analysis

Diluents: a mixture of acetonitrile and water (1:1) was prepared.

For standard preparation: 160 mg of valsartan working standard and 12.5mg of hydrochlorothiazide working standard were weighed and transferred into 200ml volumetric flask then the volume made up to 200 ml with solvent,5ml of this solution was diluted to 20 ml with the same solvent.

Sample preparation for assay and related impurities: 20 tablets were weighed and powdered then an equivalent to 160 mg of valsartan was weighed and transferred into 200ml volumetric flask and 100ml of diluents(a mixture of acetonitrile and water (1:1)) was added then sonicated for 30 minutes. After that, the volume was made up to 200 ml with the diluents, a portion of this solution is centrifuged at 3000rpm for 15 minutes, 5ml of the clear supernatant is diluted to 20 ml by diluents, and used for the analysis for assay and related impurities.

For the preparation of related impurities: (3.6 mg of USP Benzothiadiazine related compoundA, valsartan related compound A (S)-N-butyryl-N-((2-(1H-tetrazole-5-yl)-biphenyl-4-yl)-methyl1)-valine(Ivanovic, Malenovic and Jancic 2007), 6.1 mg of hydrochlorothiazide, 8.5mg of valsartan, and 20.5mg (valsartan related compound B) are placed into 100ml volumetric flask the volume made up to 100 ml with solvent which contain acetonitrile: water with the ratio (1:1), then 5ml of this solution is diluted with diluents to 100 ml, 5ml of this solution is taken and the volume made up to 50ml with solvent. This is then used for the HPLC analysis.

The samples were analysed by HPLC to confirm the amount of the active ingredients.

The high performance liquid chromatography (HPLC) apparatus consists of Thermo spectra system which is equipped with a pump (P 2000), an auto sampler spectra system (AS 3000), UV detector with UV lamp and data processor (chromquest software) the chromatographic column was Hichrom Kromasil KR, C18, (100mm x 4.6nm) containing 5µm packing L1.

The detection wavelength used was 265nm, the flow rate was 0.4ml/min, and the injection volume was 10µl.

The chromatograph is programmed as follows: A gradient elution of solution A, and B was used during the chromatographic system as indicated by the (USP) method as shown in Table (4.2).

Table (4.2): The HPLC Gradient Programmed for the Analysis of Co-Diovan

Time (minutes)	Solution A (%)	Solution B (%)	Elution
0-25	90-10	10-90	Linear gradient
25-27	10-90	90-10	Linear gradient
27-40	90	10	Isocratic

Calculations: Following are methods utilised in the calculation of assay and related impurities:

Calculation for assay: Final Concentration (F.C) for the standard was calculated by the equation:

F.C. (standard) = (Standard weight/dilution)*(dilution factor) *(assay of the standard %)* (100-water content %)*100%

Final Concentration for the Sample was calculated by the equation:

F.C. (sample) = (sample weight/dilution)* (dilution factor) *(tablet strength /tablet weight) * 100%.

Calculation for the assay of the sample was calculated by the equation:

Assay for the sample % = (Average area for the sample /F.C. for the sample) *(F.C. standard) /average area for standard) *100%

Calculation for the related impurities:

Impurity B and other impurities were calculated by the equation:

Assay = (Final concentration for impurity B/ peak area for impurity B in diluted standard) X (Peak Area for impurity B and other impurities) / (Final concentration of Valsartan in the prepared sample)] X 100%**.**

4.3.2 Plavix Analysis

Following are detailed description of plavix analysis:

Active Ingredient: 75 mg of clopidogrel bisulphate ($C_{16}H_{16}ClNO_2S$). Chemical structure Is shown in Figure (4.3) (Pereillo *et al.* 2002).

Figure (4.3): Chemical Structure of Clopidogrel Bisulphate.

Indications: Plavix is taken to prevent blood clots (thrombi) forming in hardened blood vessels (arteries).a process known as atherothrombosis, which can lead to atherothrombotic events (such as stroke, heart attack, or death).

Dosage: One tablet a day.

Price: JD 73.83 (£63**.**10) per pack which contains 28 film-coated tablets.

Manufacturer**:** Sanofi-synthelabo (France).

Thirty three samples of Plavix was collected and subjected to physical as well as chemical Analysis.

Physical testing included visual inspection of the package

Method of Analysis

The chemical analysis for Plavix (clopidogrel bisulphate) tablets was performed by using High performance liquid chromatography for assay and related impurities.

The method used was from the United States Pharmacopoeia (USP), which was verified in terms of linearity, the results indicate that this method is linear in the determination of clopidogrel in Plavix tablets, the range between 5-15 mg/100 ml, accurate, and precise**.**

Standard and Sample Preparation for Analysis

Phosphate buffer was prepared by weighing and dissolving 1.36 gram of potassium dihydrogen phosphate in 1000ml of water.

For mobile phase: a filtered and degassed mixture of phosphate buffer and acetonitrile (80:20) was prepared.

For standard preparation: 50mg of clopidogrel bisulphate was weighed and diluted in 100ml methanol, 5ml of this solution then diluted with 25ml methanol.

For sample assay and related impurities preparation: 20 tablets were powdered and weighed carefully, a portion of the powder which was equivalent to about 75mg of clopidogrel was weighed and transferred to a 100ml volumetric flask, 50ml of methanol was added and sonicated for 30 minutes then completed to volume with methanol.

A portion of this solution was filtered through 0.45µm porosity and used for the related impurities analysis.

For the analysis of the assay: 5ml of this solution was diluted to 50 by methanol, and then the solution was used for the HPLC analysis.

For related impurities: 10.35mg USP Clopidogrel Related Compound A,15.15mg USP Clopidogrel Related Compound C and 2ml stock Clopidogrel Bisulphate stock standard were added to 50ml volumetric flask, volume was completed to 50 ml with methanol, then 5 ml of this solution volume made up to 200 ml with mobile phase. And used for the analysis of related impurities of HPLC.

The high performance liquid chromatographic system (HPLC) apparatus (TSP4) which consists of Thermo spectra system which is equipped with a pump (P2000), an auto sampler spectra system As (3000), UV detector with UV lamp, and data processor, the chromatographic column was Ultron ES-OVM, 150*4.6mm, 5µm and Pre-column: ES-OVM, 10*4mm.

The detection wavelength used was 220-nm; the flow rate was 1.0 ml per minute. The injection volume was 10µL.

Calculations: Following are methods utilised in the calculation of assay and related impurities:

Calculation for assay: Final Concentration (F.C) for the standard was calculated by the equation:

F.C. (standard) = (Standard weight/dilution)*(dilution factor)*(assay of the standard %)* (100-water content %) * (419.9/321.82) * 100%.

Where 321.82 is the molecular weight of clopidogrel; 419.90 is the molecular weight for bisulphate.

Final Concentration for the Sample was calculated by the equation:

F.C (sample) = (sample weight /dilution)* (dilution factor)* (tablet strength /tablet weight) * 100%

Calculation for the assay of the sample was calculated by the equation:

Assay for the sample % = (Average area for the sample /F.C. for the sample) *(F.C. standard) /average area for standard) *100%

Calculation for the related impurities:

Final Concentration for diluted standard was calculated by the equation:

F.C (diluted Standard) = (standard weight/ dilution) *(dilution factor) * (assay for the standard %) * (100-content of water %)*(419.9/321.82)*100%

Final Concentration for sample for related impurities was calculated by the

Equation:

F.C. (sample)= (sample weight/dilution) * (tablet strength/ Tablet weight) *(419.9/321.82)* 100%

Calculation for assay for impurity A was calculated by the equation:

Assay for impurity A = (average area for impurity A / F.C. for the related sample) * (F.C for Imp. A in the diluted standard / average area for Imp. A for the diluted standard)*100%

Calculation for impurity C was calculated by the equation:

Assay for Impurity C= (Impurity C average area/ F.C. for the related sample) * (F.C for diluted standard/ average area for the diluted standard) *100%

4.3.3 Concor Analysis

Active Ingredients: 5mg of Bisoprolol Fumarate [$(C_{18}H_{31}NO_4)_2.C_4H_4O_4$].

Chemical structure is shown in Figure (4.4) (USP Monograph 2007).

Figure (4.4): Chemical Structure of Bisoprolol Fumarate.

Indications: Treatment of high blood pressure (hypertension). Coronary heart disease (angina pectoris).

Dosage: One tablet a day.

Price: JD 5.64 (£4.80) per Pack, which contains 30 film-coated tablets.

Manufacturer: Merck (Germany).

Thirty three samples of Concor were collected from Amman. These samples were subjected to physical as well as chemical analysis.

Physical testing of Concor was conducted by visual inspection of the package.

Method of Analysis

The chemical analysis of Concor was performed by using high performance liquid chromatography for determination of bisoprolol assay as well as its related impurities.

The method used was from the United States Pharmacopoeia (USP), which was validated by the work performed by JPM in terms of linearity, the results indicate that this method is linear in the determination of bisoprolol fumarate in Concor tablets, the range between 3.02-9.06 mg/100 ml, accurate, and precise.

Standard and Sample Preparation for Analysis

The buffer was prepared by dissolving 0.01M potassium dihyhdrogen phosphate in 1000ml water adding 0.1% v/v triethylamine, the pH was adjusted to 5.5 by 10% phosphoric acid.

One Litre of mobile phase was prepared by using 570ml of the buffer and 430ml of methanol.

For standard preparation: 50mg of bisoprolol fumarate working standard were weighed and dissolved in 50 ml water, then 3ml of this solution was diluted in 50 ml mobile phase.

Sample preparation for assay and related: 20 tablets were weighed and powdered then an equivalent to 50 mg of bisoprolol fumarate was dispersed with 10 ml water and the volume was completed to 50 ml by adding mobile phase, then sonicated for 15 minutes, and centrifuged at 4000 rpm for 15 minutes, then the supernatant were used for related analysis, and for the assay analysis 3ml from this solution was diluted to 50ml with mobile phase.

Diluted standard preparation: 50 mg of bisoprolol fumarate working standard were weighed and dissolved in 50ml water, 5ml of this solution was diluted to 50 ml with water, and further dilution of 5ml of this solution to 100ml with mobile phase was made.

The high performance liquid chromatography (HPLC) apparatus consists of Thermo spectra system which is equipped with a pump (P 1000), an auto sampler spectra system (AS

3000), UV detector with a UV lamp, and data processor, the chromatographic column was Hypersil, BDS, C18, 5 µm, 250*4.6 mm.

The detection wavelength used was 225nm, the flow rate was 1.0 ml/min, and the injection volume was 20µl.

Calculations: Following are methods utilised in the calculation of assay and related impurities:

Calculation for assay: Final Concentration (F.C) for the standard was calculated by the equation:

(Standard weight/dilution)*(dilution factor)*(assay of the standard %)* (100-water content %)*100%

Final Concentration for the Sample was calculated by the equation:

Final concentration for the sample = (sample weight/dilution)* (dilution factor) *(tablet strength /tablet weight) * 100%

Calculation for the assay of the sample was calculated by the equation:

Assay for the sample % = (Average area for the sample /F.C. for the sample) *(F.C. standard) /average area for standard) *100%

Calculation for the related impurities:

Final Concentration for diluted standard was calculated by the equation:

Final Concentration (diluted Standard) = (standard weight/ first dilution)* (dilution factor) * (assay for the standard %) * (100-content of water %) *100%

Final Concentration for sample for related impurities was calculated by the equation:

Final concentration for related sample = (sample weigh/dilution) * (tablet strength/ tablet weight) * 100%

Calculation for assay for maximum impurity was calculated by the equation:

(Maximum impurity average area/ F.C. for the related sample) * (F.C for diluted standard/ average area for the diluted standard) *100%

Calculation for total impurities was calculated by the equation:

(Total impurities average area/ F.C. for the related sample) * (F.C for diluted standard/ average area for the diluted standard) *100%

4.3.4 Lipitor Analysis

Active Ingredients: Each tablet contains 21.69 mg. atorvastatin calcium.

Chemical structure is shown in Figure (4.5) (USP 2011).

Figure (4.5): Chemical Structure of Atorvastatin Calcium

Indications: For reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides.

Dosage: The usual starting dose is 10mg. once a day; the maximum dose is 80mg. a day.

Price: JD 47.68 (£ 40.75) per pack which contains 30 film-coated tablets.

Manufacturer: Parke-Davis (Germany).

Thirty three samples of Lipitor were collected and subjected to Physical and chemical tests. Chemical testing for Lipitor was conducted using HPLC and an additional test called Dissolution testing.

Physical testing of Lipitor was conducted by visual inspection of the package.

1-Method of HPLC Analysis

The analysis of Lipitor was performed by using high performance liquid chromatography for determination of atorvastatin calcium in Lipitor for assay as well as its related impurities.

The method employed was from the United States Pharmacopoeia (USP), which was validated by the work performed by JPM in terms of linearity, the results indicate that this method is linear in determination of atorvastatin in Lipitor in the range between 5.00-15.01 mg/100 ml, accurate within the same range, and precise.

Standard and Sample Preparation for Analysis

Mobile phase preparation: Phosphate buffer was prepared by weighing 6.8 gram of potassium dihydrogen phosphate and transferring it to 1000 ml of water, and adding 1 ml of triethylamine and the then the buffer is filtered through 0.45 µm membrane filter and degassed. For mobile phase: a filtered and degassed mixture of phosphate buffer, acetonitrile, and methanol (5:5:3) was prepared, pH was adjusted to 4.0 by phosphoric acid.

For standard preparation 55 mg of atorvastatin calcium working standard was dissolved in 50 ml methanol, 5 ml of this solution is diluted to 50 ml by adding a solution prepared with methanol and water in the ratio 1:1 which means 50% methanol.

Sample preparation for assay and related: 5 tablets were powdered and transferred into 100 ml volumetric flask 10 ml of water was added to disperse then the volume completed with methanol, then sonicated for 30 minutes with frequent shaking and centrifuged at 4000 rpm for 15 minutes, for related analysis the supernatants were used and for assay analysis further dilution is performed by diluting 5 ml of this solution to 50 ml with 50% methanol.

Diluted standard preparation: 40 mg of atorvastatin calcium working standard were weighed and dissolved in 100 ml of methanol and 4 ml of this solution diluted to 100 ml with the same solvent.

The high performance liquid chromatography (HPLC) apparatus consists of Thermo spectra system which is equipped with a pump (P 1000), an auto sampler spectra system (AS 3000), UV detector with a UV lamp, and data processor.

The chromatographic column was Hypersil, BDS, C18, 5µm, 250*4.6 mm.

The detection wavelength used was 248 nm, the flow rate was 1.5 ml/min, and the injection volume was 20µl.

Calculations: Following are methods utilised in the calculation of assay and related impurities:

Calculation for assay: Final Concentration (F.C) for the standard was calculated by the equation:

F.C. (standard) = (Standard weight/dilution)*(dilution factor)*2(558.65/1155.42) *(assay of the standard/100)* (100-water content/100)*100%

(Where 558.65 and 1155.42 are the molecular weight of anhydrous atorvastatin and atorvastatin calcium respectively).

Final Concentration for the Sample was calculated by the equation:

F.C. (sample) = (sample weigh /dilution)* (dilution factor) *(tablet strength) /tablet weigh) * 100%

Calculation for the assay of the sample was calculated by the equation:

Assay for the sample % = (Average area for the sample /F.C. for the sample) *(F.C. standard) /average area for standard) *100%

Calculation for the related impurities:

Final Concentration for diluted standard was calculated by the equation:

F.C. (diluted Standard) = (standard weight/ first dilution) *(dilution factor) *2(558.65/1155.2) * (assay for the standard %) * (100-content of water %) *100%

Final Concentration for sample for related impurities was calculated by the Equation:

F.C. (sample) = (sample weight/dilution) * (tablet strength/ weight) * 100%

Calculation for assay for maximum impurity was calculated by the equation:

Max. Imp. % = (average area for the maximum impurity/ F.C. for the related sample) * (F.C for diluted standard/ average area for the diluted standard) *100%

Calculation for total impurities was calculated by the equation:

Tot. Imp. %= (total impurities average area/ F.C. for the related sample) * (F.C for diluted standard/ average area for the diluted standard) *100%.

2- Lipitor Dissolution Analysis

In order to evaluate the formulation effectiveness dissolution was performed on Lipitor since atrovastatin is poorly soluble and special care with formulation and manufacturing parameters is a must to insure atrovastatin tablets compliance to the required standards of solubility.

Method of Dissolution Analysis

The method employed was from the United States Pharmacopoeia (USP), which was validated by the work performed by JPM in terms of linearity, the relation between the final concentration of atorvastatin and the first derivative response of solution is linear within the range 0.5-4.0 mg/100 ml, accurate within the same range, and precise.

The method proved to be accurate, precise and could be used as alternative to the (USP) method.

Buffer Preparation**:** the medium used was phosphate buffer which was prepared by dissolving 1.38 gram of sodium dihydrogen phosphate and 20 grams of dodecyl sodium phosphate in 900 ml water and pH was adjusted to 7.0 by adding 1M sodium hydroxide then the volume completed with water to 1000 ml.

- Apparatus 2 (Paddle), 75 rpm.
- Acceptable limit; not less than 80% Dissolved in 60 minutes.
- Measure first Derivative. = 296 nm.
- The standard was prepared by weighing and dissolving 120 mg. Atorvastatin calcium working standard, in 100 ml methanol, and then diluted with 100 ml buffer.

For sample preparation: 6 tablets were introduced into the dissolution vessels, after 60minutes a portion of the dissolution was centrifuged for 15 minutes at 4000 rpm, and the supernatant was used for the analysis, the first derivative of these sample preparations and the standard preparation were measured at about 296 nm, scan speed was 1200nm/min.

The apparatus used was Beckman Coulter (USA), Du 640i, and spectrophotometer.

Calculations for Dissolution of Lipitor:

Final Concentration of the standard was calculated by the equation:

F.C. (standard) = (standard weight/dilution)*(dilution factor)*2(558.65/1155.42)* assay%* (100-content of water %)*100%

A% standard = (average absorbency for standard /average F.C. standard)*1000

Final concentration for the sample was calculated by the equation:

(Sample strength / dilution)*100%.

F.C. (sample) = (tablet strength /900)*100%

Drug release of the sample = (average absorbency for sample/ average F.C. for sample)* (1/A %)* 100000.

4.4 Analysis of Phase Two

This phase consisted of forty samples of Concor which were collected from pharmacies from Amman, Irbid and Zarka.

Concor was subjected to Physical and Chemical tests. The active material in the drug is bisoprolol fumarate. The analysis of Concor is performed using high performance liquid

chromatography for determination of bisoprolol assay as well as its related impurities as discussed in the analysis of Concor in phase one.

4.5 Analysis of Known Counterfeit Samples

Samples of counterfeit medicines were obtained from Jordan Food and Drug Administration (JFDA). According to (JFDA) officials, these samples were previously confiscated from different pharmacies. Medications obtained are: Plavix, Concor, and Lipitor, but Co-Diovan was not available.

Physical appearance was inspected and chemical analysis was performed as follows:

4.5.1 Plavix Analysis: Two samples were obtained and were subjected to physical and chemical analysis.

Physical testing of Plavix included visual inspection of the packages.

The chemical analysis of Plavix (clopidogrel) tablets was performed using high performance liquid chromatography for assay and related impurities. The method used was validated and employed as discussed in the analysis of Plavix in phase one.

4.5.2Lipitor Analysis: Two samples were obtained from the Jordan Food and Drug Administration (JFDA), the customs authority previously confiscated one and the other one was confiscated from the market. These samples were subjected to three tests:

Physical, chemical, which included HPLC and dissolution testing.

Physical testing of Lipitor included visual inspection of the packages.

The chemical analysis methods were validated and employed as discussed in the analysis used for Lipitor in phase one.

4.5.3 Concor Analysis

One sample obtained from Jordan Food and Drug Administration (JFDA), which was previously confiscated from the market. This sample was subjected to physical and chemical analyses. The physical testing including visual inspection of the package.

The active material in the drug is bisoprolol fumarate. The chemical analysis of Concor is performed by using high performance liquid chromatography for assay and related impurities. The method used was from the United States Pharmacopoeia (USP), which was modified and validated before applicationas discussed in the analysis of Concor in phase one.

4.6 Identification Analysis for the Samples of Known Counterfeit Medications

The following tests are considered as useful in identifying counterfeit pharmaceuticals since other possible tests for minor excipients would not be as discriminating as these tests. Therefore further analysis for the identification of the ingredients was performed as follows:

Concor average weight ranges from 136.8 mg to 139.4 mg.

Lipitor average weight ranges from 288 mg to 307 mg.

Plavix average weight ranges from was 250 mg to 257 mg.

4.6.1 Identification of Starch

Using the British Pharmacopoeia, 10 tablets were powdered, one gram of the powder was put in a flask and 50 ml of water were added and boiled for one minute then cooled. The result was thick, gluey and cloudy solution 0.05 ml of iodine solution was added to 1ml of the mucilage. The result was an orange-red to dark blue colour which is an indication of the presence of starch in the formula which disappears on heating.

4.6.2 Identification of Lactose: British Pharmacopoeia method was used to identify the existence of lactose in the formula.

10 tablets from the original and counterfeit samples were powdered and 0.25 gram was added to 5 ml of water and 5 ml of ammonia. The mixture was heated in a water-bath at 80 C for 10 minutes.

If the lactose is present in the formula, a red colour develops.

4.6.3 Identification of Hydroxypropylcellulose: British Pharmacopoeia method was used to identify the existence of hydroxypropylcellulose in the formula.

10 tablets were powdered and one gram of the powder was added into 50 gram of carbon dioxide-free water, then the mixture was heated to 90 C and allowed to cool, then adjusted to100 gram with carbon dioxide-free water, and stirred until dissolution is completed.

10ml of solution, 0.3 ml of diluted acetic acid, and 2.5ml of a 100 gram solution of tannic acid were added together.

If the hydroxypropylcellulose exists then a yellowish-white flocculent precipitate is formed which dissolves in dilute ammonia.

CHAPTER FIVE

RESULTS OF KNOWN COUNTERFEIT PHARMACEUTICALS

Chapter Five

5. Results of Known Counterfeit Pharmaceuticals

Samples of counterfeit medicines were obtained from Jordan Food and Drug Administration (JFDA). According to (JFDA) officials, these samples were previously confiscated from different pharmacies. Medications obtained are Plavix, Concor and Lipitor, while Co-Diovan was not available.

Physical appearance was inspected and chemical analysis was performed as described in chapter 4, and following are the results.

5.1 Results of Analysis of Known Counterfeit Plavix

Two samples were obtained and subjected to physical and chemical analysis.

5.1.1 Results of Physical Testing: Visual inspection showed that both packages have the same batch number but different expiry dates. The packaging for each sample is almost the same as the genuine medicine except that one of the counterfeit samples had different colour from the genuine one. Both counterfeit samples have no hologram as shown in figure (5.1).

The letters on the packages have the same font size and colour. It was obvious that the technology used in manufacturing of the final packaging is high technology and the counterfeiters put a lot of effort trying to imitate the colour, size, and everything related to the final production of the product in order to deceive the public as well as the authority by

duplicating the original packaging. Even the batch number of the counterfeit samples has four digits numbers the same as the original sample.

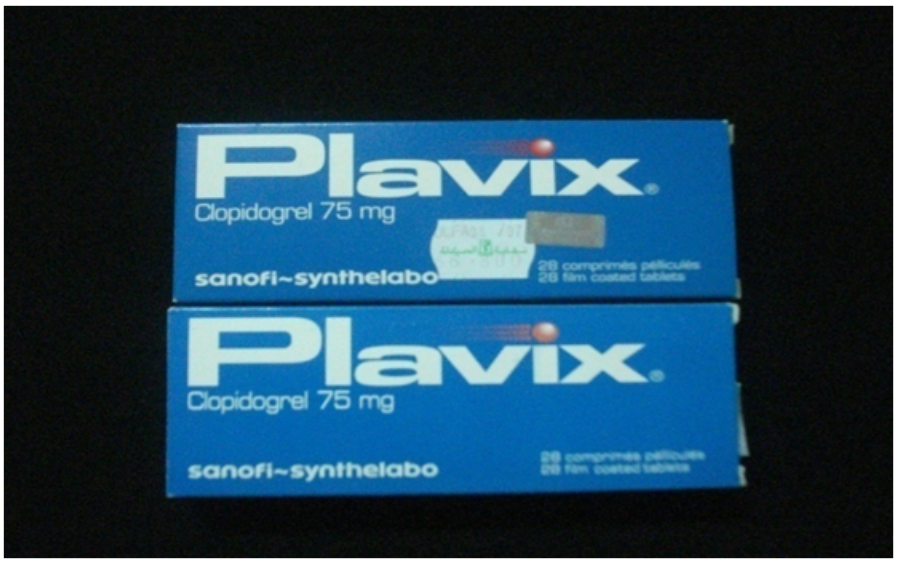

Figure (5.1): A Comparison between Genuine and Counterfeit Plavix

(The genuine medicine is on the top while the counterfeit one is on the bottom**)**

Looking at blisters, there seems to be no differences except that the font used in the counterfeit drug was a little bit larger than the one used in the genuine medicine, as shown in figure (5.2).

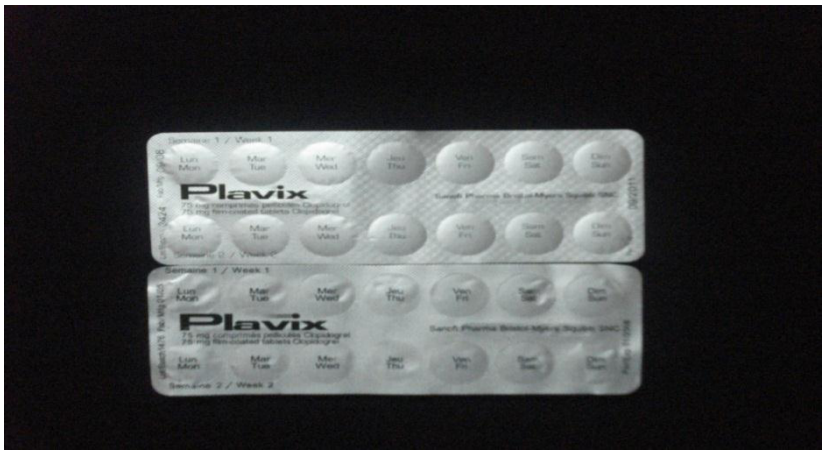

Figure (5.2): A Comparison between Genuine Blister and Counterfeit Blister of Plavix

(Blisters of the genuine medicine on the top and the counterfeit one on the bottom)

Test on tablets was performed by weighing the counterfeit tablets and the original ones and comparing the shape, color, and the size of the counterfeit tablets and the original ones, as shown in figure (5.3).

Figure (5.3): A Comparison between Genuine and Counterfeit Plavix tablets

(The genuine tablet is shown on the right and the counterfeit tablets D200, D201 are on the left).

As shown in figure (5.3), one counterfeit tablet sample D200 has a different colour from the original. It was noticed that, the counterfeit tablet D 200 was hard to powder and when it was crushed, the powder turned to granules. The range of the weight of the tablets was 250 mg to 257 mg compared to the range of the original, which was between252 mg and 256.9 mg for each tablet which constitutes a slight difference but not statistically significant.

The other sample (D201) which looks like the original, but when powdered, it looks like granules not powder, and the tablets weigh more than the genuine one with wide range from 270 mg to 280 mg.

5.1.2 Results of Chemical Analysis

A result of Chemical analysis of the confiscated samples of Plavix which was obtained from (JFDA) is shown in Table (5.1).

.

Table (5.1): Results of Assay and Related Impurities Testing of Counterfeit Plavix.

USP acceptance limits for Plavix are given in the boxes below

90%≤ Assay limit ≤110%.

Impurity A ≤ 1.2%

Impurity C ≤ 1.5%

Sample ID	Batch No.	Manuf. Date	Expiry. Date	%Assay	Impurity A %	Impurity C %
Plavix original	2359	4-2008	4-2011	101.7	0.05	0.49
Plavix D200	1476	01-2005	01-2008	4.6	0	0
Plavix D201	1476	02-2006	02-2009	0	0	0

As shown in table (5.1) results indicated that D201 sample has zero active ingredients the sample labeled D200 , s shown in Table (5.1),clopidogrel related ((S)-(ochlorophenyl)-6,7-dihydrothieno[3,2-c] pyridine5(4H)-acetic acid, Hydrochloride. Chemical structure is shown in figure (5.4) (Mohan *et al.*2008).

Figure (5.4) Chemical Structure of Clopidogrel Related Impurity A.

and Related impurities achiral isomer of clopidogrel named as clopidogrel related compound C is Methyl(-)-R-(ochlorophenyl)-6,7-dihydrodtheino [3,2-c] pyridine-5(4H)-acetate, hydrogen sulphate. Chemical structure is shown in figure (5.5) (Mohan *et al*. 2008).

Figure (5.5) Chemical Structure of Clopidogrel Related Impurity C.

Comparison between genuine and counterfeit samples of Plavix

Figure (5.6) shows the HPLC chromatogram of genuine Plavix and figures (5.7) and (5.8) show HPLC chromatogram for counterfeit samples D200 and D201 sample.

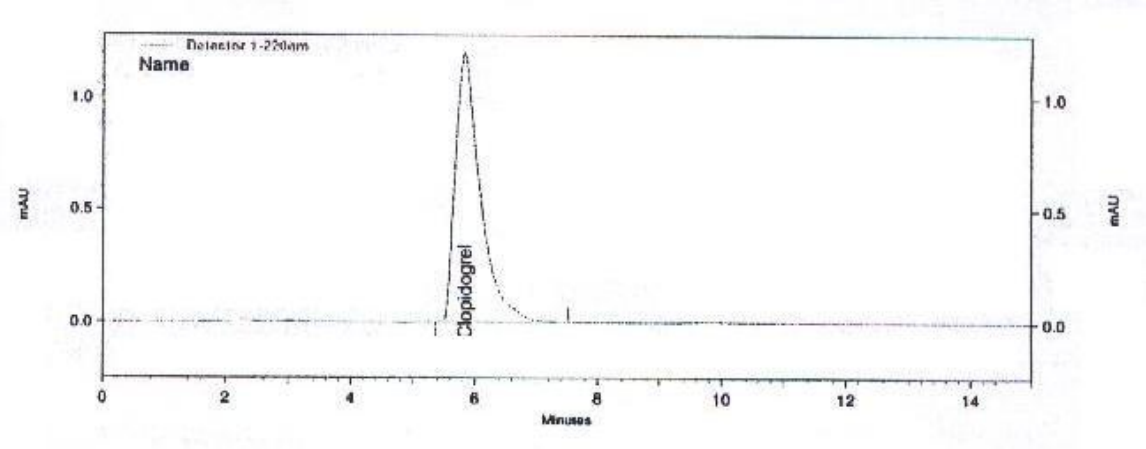

Figure (5.6): HPLC Chromatogram Showing the Active Ingredient (Clopidogrel) in the Original Medicine

As indicated in the figure above, the retention time for the active ingredient (clopidogrel) is around 6 minutes.

Figure (5.7) illustrate the Chromatogram of the counterfeit sample (D200).

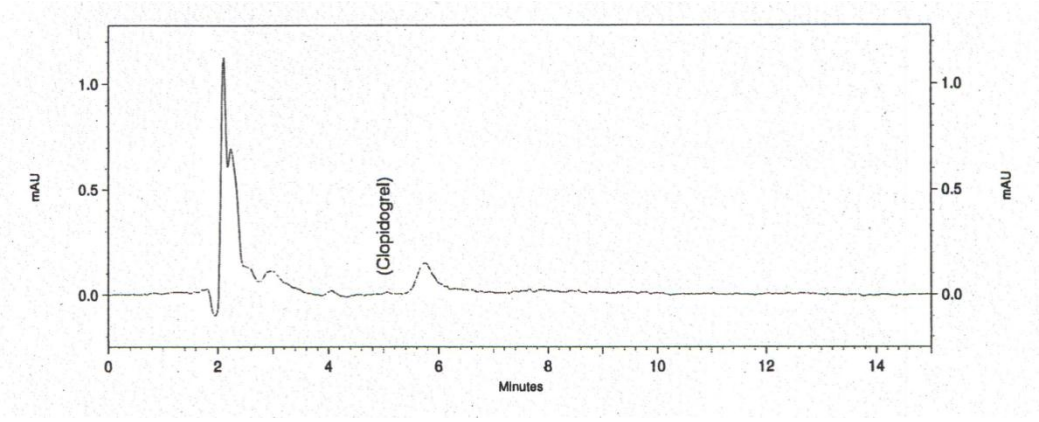

Figure (5.7) Counterfeit Medicine Coded D200.

The figure indicates that a very small amount of the active ingredeintis noticed as indicted by the retension time which is around 6 minutes for the original while unknown peak was noticed at around 2 minutes.

Figure (5.8) illustrate the chromatogram for the counterfeit sample coded D201.

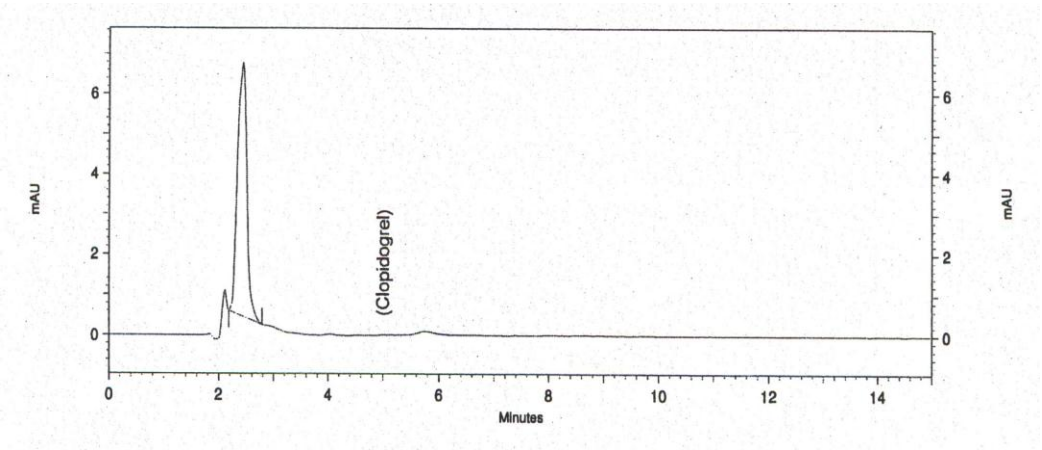

Figure (5.8): Counterfeit Medicine coded D201.

The chromatograms of the counterfeit sample (D201) as shown in the figureis not colpedogril as indicted by the retention time. There is no peak around 6 minutes retention time.

HPLC chemical analysis indicated that there was no active ingredient found in D201 and only4.6% active ingredient found in D200 which is supposed to be not less than 90% in this medicine which is widely used in Jordan in artery operations as post operation medication to prevent depositions in arteries.

5.2 Results of Analysis of Known Counterfeit Lipitor

Two samples of Lipitor were obtained from the Jordan Food and Drug Administration (JFDA), one was confiscated by the customs authority and the other was confiscated from a pharmacy and these samples were subjected to three tests:

5.2.1 Results of Physical Testing: Visual inspection of the packages showed that the two samples have different batch numbers with different expiry dates. Inspecting batch numbers of both counterfeit samples indicated that they have the same seven digits format, which is the same digit as the original one.

The packaging of counterfeit sample looks the same as the genuine one; even the colour of the printing and the font size of the printing is the same as the genuine packaging. The shape and the color of the counterfeit tablets are almost the same as the genuine medicine which makes it hard to distinguish between the counterfeit and the original medicine, as shown in figure (5.9).

Figure (5.9): A Comparison between Genuine and Known Counterfeit Lipitor

(The genuine medicine on the right and the known counterfeit one on the left).

Inspecting the blisters of the counterfeit medicines indicated that it was very hard to distinguish between the counterfeit and the genuine medicine as shown in figure (5.10).

Figure (5.10): A Comparison between Genuine and Known Counterfeit Blisters of Lipitor.

(The genuine blister on the left, the known counterfeit blister on the right).

As shown in figure (5.11), the colour, size and shape of the counterfeited tablets were the same as the original ones. It also showed that, the weight of the counterfeit tablet ranged from 276 to 288 mg which is significantly less than the genuine one (303 to 318 mg). The weight of the second sample of counterfeit drug was between 288 to 307 mg, which is slightly, less than the genuine one.

Figure (5.11): A comparison between Genuine and Known Counterfeit Lipitor Tablets

(The genuine tablet is on the right and the known counterfeit tablets are on the left).

The physical appearance of the confiscated samples obtained from (JFDA) looks like the original package. This fact made it harder for the authority to distinguish the counterfeit from the original pharmaceutical. This result confirms the fact that counterfeiters usually utilise very sophisticated technology for manufacturing and packaging. The counterfeiters pay a great attention to the details of the outer package in an attempt to deceive consumers, the authority and any buyers into believing that these products are original, so the printing font size and colour of the package and the printing is imitated exactly.

5.2.2 Results of Chemical Analysis of Lipitor

Lipitor was subjected to two chemical analyses:

Results of HPLC Analysis: HPLC analysis of Lipitor is shown in table (5.2).

Table (5.2): Results of Assay and Related Impurities Testing of Known Counterfeit Lipitor (20mg).

USP acceptance limits for Lipitor are given in the boxes below.

90%≤ Assay limit ≤110%.

Maximum Impurity ≤ 1.5%

Total Impurities ≤ 3.5%

Sample ID	Batch No.	Manuf. Date	Expiry Date	% Assay	% Max. Imp.	% Total Imp.
Gen. Lipitor	0330088	3-2008	2-2011	99.1	0.26	0.65
Lipitor B200	0359045	04-2005	03-2008	73.59	0.11	1.94
Lipitor 201	0195036	03-2006	02-2009	72.49	0.30	0.67

Table (5.2) shows a comparison between the active ingredient amount in both the genuine and the counterfeit Lipitor. It shows that the samples contain the active ingredients but with quantities below the pharmacopoeial limits which classifies these samples as substandard products. It was noticed that the counterfeit sample (B200) has an amount of active ingredient of (73.59%) and B201 has the amount of (72.49%) while the original medicine has (99.1%) as depicted in the following figures.

The related impurities in Lipitor are Atorvastatin amide, Desfluoro Atorvastatin, Diastereoisomer, O-methyl Atorvastatin, Atorvastatin lactone and Atorvastatin methyl ester (Mornar, Damic and Nigovic 2010).

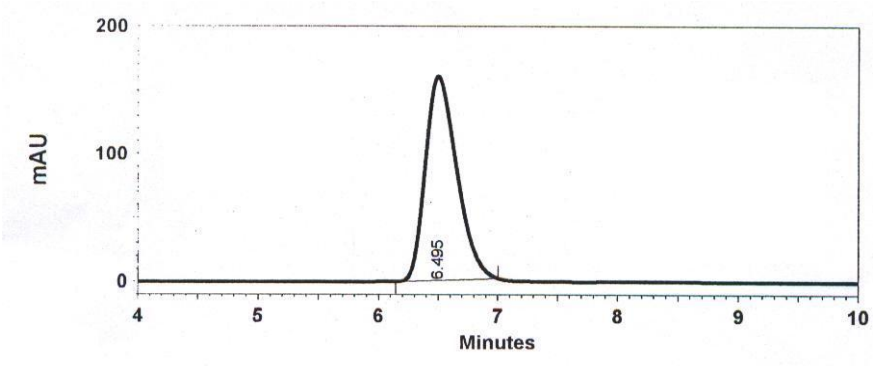

Figure (5.12): HPLC Chromatogram Showing Active Ingredient (Atorvastatin) in Genuine Lipitor

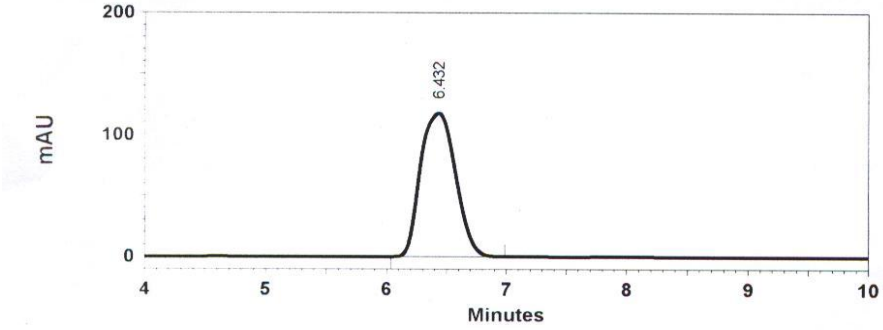

Figure (5.13): HPLC Chromatogram of Known Counterfeit Lipitor Coded B 200

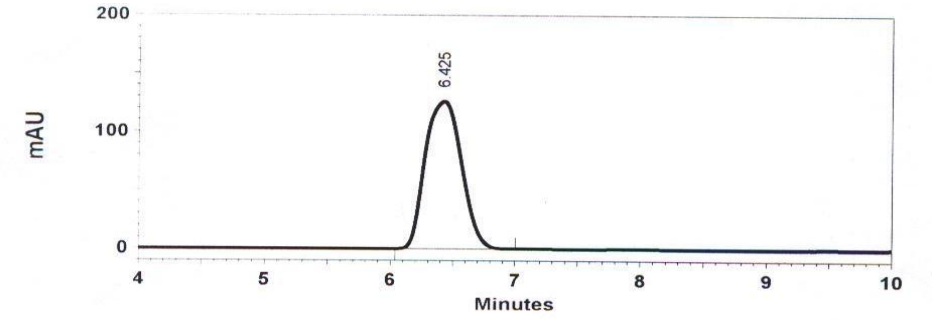

Figure (5.14): HPLC Chromatogram of Known Counterfeit Lipitor Coded B201

The above three figures indicated that the retention time and the UV-absorption recorded on the peak indicate that the active ingredient is atorvastatin but the quantity of the active ingredient was different from the original as noticed by the height of the peaks. This is a typical example of counterfeit medicine characterised by wrong quantity of active ingredients. This sample failed the specification in terms of content, which is less than the acceptable limits noticed by the (HPLC) analysis, as shown in the figures 5.12– 5.14.

Results of Dissolution Analysis

In order to evaluate the formulation effectiveness, a dissolution test was performed on Lipitor since atorvastatin is poorly soluble and special care with formulation and manufacturing parameters is required to insure atorvastatin tablets compliance with the required standards of solubility.

Dissolution test is frequently used to measure the stability of the drug. It measures the amount of the drug available to the body (bioavailability). In this sense dissolution test is a quality control test which the drug must pass in order to be authorized for use in the market. As shown above there are differences between the two samples. The two samples were analysed for their drug release and the results are in table 5.3.

Table (5.3): Results of Dissolution Testing of Known Counterfeit Lipitor (20mg)

% Drug Release Limit ≥ %80

Sample ID	Batch No.	Manuf. Date	Expiry Date	%Drug Release
Lipitor Gen.	0330038	3-2008	2-2011	101.6%
Lipitor B200	0359045	04-2005	03-2008	79.145%
Lipitor B201	0195036	03-2006	02-2009	29.714%

Dissolution tests have shown a large non- controlled practice for one of the samples (B201) as shown in table (5.3) where the percentage of the drug release was 29.7%, which is below the pharmacopoeial limit of 80%. This illustrates the tendency of counterfeiters to pay great attention to the appearance of the final product.

Results on the other hand, have indicated that sample (B200) as shown in table (5.3) has a much lower degree of bioavailability since drug release was below the pharmacopoeial limits of only one percent. These results indicate that two different manufacturers produced the two batches.

In summary, dissolution tests for Lipitor seem to indicate a large variability in the process, which ranges from simply a substandard to a completely counterfeited pharmaceutical in this sample. These results showed the extent to which counterfeiting is dangerous to human life.

Sample 1: (B200) showed less than the acceptable percentage limit of drug release79.145% which was slightly lower than the United States Pharmacopoeia limit and old expiry date which made it close to original (80% or over).

Sample 2: (B201) showed a very poor dissolution profile and a very low release percentage of active ingredients 29.7%.These results may be attributed to the formulation employed and/or to the storage conditions.

Dissolution tests indicate large non- controlled practice for one of the samples (B201). The other sample only has an assay value of 73.6% and has a percentage release of 79.1% compared with the claimed figure. Although B200 may be less than ideal if consumed by a patient, B201 would be far worse as the patient would receive very little active drug.

5.3 Results of Analysis of Known Counterfeit Concor

One sample was subjected to physical and chemical analysis.

5.3.1 Results of Physical Testing: Visual inspection of the package showed that the known counterfeit package looks exactly as the original package. As seen in figure (5.15) the package has the same size and the printing colour and the same font size of printing as the original one which makes it hard to distinguish between the counterfeit and the original package.

Figure (5.15): A Comparison between Genuine and known Counterfeit Concor

(The genuine medicine on the top and the known counterfeit on the bottom).

It was obvious that the counterfeiters paid a lot of attention to the very specific details on the outer package, the font size printing, the colour of the package, and the logo of the manufacturing company using high technology to imitate these products. The only difference noticed was that genuine Concor has a six digit batch number while the counterfeit package has seven digits.

The shape of the tablets has a heart-shaped form which is usually hard to imitate without very specialised tools. When crushing the tablets for the analysis, the researcher noticed that crushing was very hard and the final powder is granular unlike the original powder. In addition, original tablets have white colored powder while the counterfeited ones were yellow. When weighing the tablets, the counterfeit tablets weighed less than the original

tablets. Their weight ranges from 136.8 mg to 139.4 mg while the original weighs 171mg to 173.9 mg. The colour, size and shape of the tablets was also compared and found to have the same as the original

The colour and shape of the tablets is shown in figure (5.16)

Figure (5.16): A Comparison between Genuine and Known Counterfeit Concor tablets

(The genuine tablet is on the right and the known counterfeit tablet on the left)

5.3.2 Results of Chemical Analysis of Concor

Chemical analysis showed no active ingredients available in A200 as shown in table (5.4). This result indicates a very serious problem for the patients who think that their blood pressure is actually being regulated by taking these zero active ingredient pharmaceuticals

Table (5.4) shows a comparison between the active ingredient amount in both the genuine and the counterfeit Concor.

Table (5.4): Results of Assay and Related Impurities Testing of Known Counterfeit Concor

USP acceptance limits for Concor are given in the boxes below.

90%≤ Assay limit ≤110%.

Max. Impurity ≤0.25%

Total Impurities ≤ 1.0%

Sample ID	Batch No.	Man. Date	Expiry Date	%assay	% Max. Imp	% Total Imp.
Concor Gen.	101071	2-2009	1-2012	99.5	0.03	0.11
Concor A200	3723703	09-2006	08-2009	0	0	0

As shown in table (5.4) there is no active ingredient in the sample obtained from (JFDA). Figures (5.17) and (5.18) show a comparison between (HPLC) chromatogram regarding the active ingredient amount in both the genuine and the counterfeit concor.

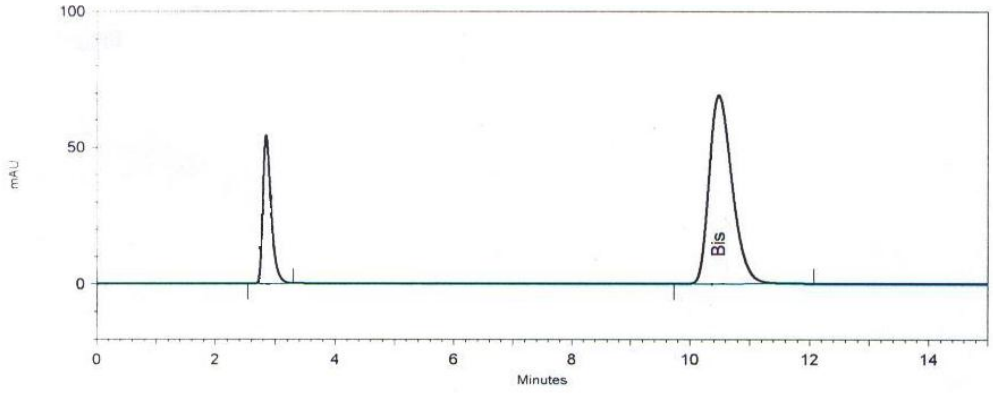

Figure (5.17): HPLC Chromatogram showing the active ingredient (Bisoprolol Fumarate) of the Genuine Medicine.

Figure (5.17) illustrates the existence of the active ingredients in the genuine Concor (bisoprolol fumarate) in the second peak; while figure (5.18) shows that there is no active ingredient in the counterfeited medicine. Instead, there are two un- identified peaks observed at different retention times.

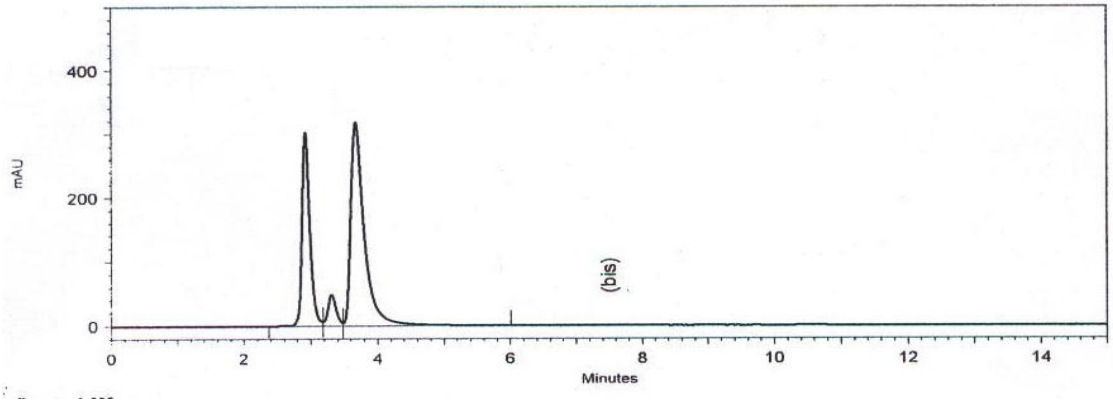

Figure (5.18): HPLC Chromatogram of the Known Counterfeit Medicine.

The related impurities for concor are Bisoprolol Dibenzylether, Bisoprolol n-propoxy-isomer, Bisoprolol derivative Diphenyl methane, Bisoprolol Benzylalcohol and Bisoprolol derivative Z/E-olefin (USP 2006).

The chromatogram of the counterfeit sample indicated that it contains the wrong ingredeint. The substance presented in this sample is not Bisoprolol, as shown by the retention time of the original sample. There is no peak around 10 minuts retention time.

Therefore, after conducting the (HPLC) analysis, the sample was classified as counterfeit based on the absence of the active ingredient (bisoprolol fumarate) in the sample.

5.4 Results of Identification Analysis for the Samples of Known Counterfeit Medications

The following tests are considered as useful in identifying counterfeit pharmaceuticals since other possible tests for minor excipients would not be as discriminating as these tests. Therefore, further analysis for the identification of the ingredients was performed as follows:

5.4.1 Results of Identification of Starch

The results are presented in table (5.5).

Table (5.5): Results of Starch Identification in the Original and Known Counterfeit Samples.

Sample ID	Colour	Contain starch
Lipitor original	Light brown	No
Lipitor B200	Light brown	No
Lipitor B201	Orange-red to dark blue	yes
Plavix Original	Light brown	No
Plavix D200	Orange-red to dark blue	Yes
Plavix D201	Orange-red to dark blue	Yes
Concor Original	Orange-red to dark blue	Yes
Concor A200	Orange-red to dark blue	Yes

As shown in Table (5.5) Lipitor B201 contains starch, a component that does not exist in non-counterfeited Lipitor.

For Plavix, results of analysis in Table (5.5) indicated that the original sample does not contain starch while the two counterfeited samples do contain starch.

Finally, results indicated that Concor has starch in both original and the counterfeit samples.

These results confirm what has been found in previous studies that most counterfeited drugs contain starch instead of active ingredients and other excipeints that should be found in the formula.

5.4.2 Results of Identification of Lactose

The results are presented in table (5.6).

Table (5.6): Results of Lactose Identification in the Original and Known Counterfeit Samples.

Sample ID	Colour	Lactose
Lipitor Original	red	Yes
Lipitor B200	Pink to red	Yes
Lipitor B201	white	No
Plavix Original	white	No
Plavix D200	white	No
Plavix D201	white	No
Concor Original	White	No
Concor A200	white	No

The results of the analysis as shown in table (5.6) indicted that among all samples used in this analysis, only Lipitor original and b200 have lactose.

5.4.3 Results of Identification of Hydroxypropylcellulose: British Pharmacopoeia method was used to identify the existence of hydroxypropylcellulose in the formula.

The results are presented in table (5.7).

Table (5.7): Results of Hydroxypropylcellose Identification in the Original and Known Counterfeit Samples.

Sample ID	Colour	Existence of Hydroxypropylcellulose
Lipitor Original	Yellowish-white	Yes
Lipitor B200	Yellowish-white	Yes
Lipitor B201	Yellowish-orange	No
Plavix Original	Yellowish-white	Yes
Plavix D200	Yellowish-orange	No
Plavix D201	Yellowish-orange	No
Concor Original	Yellowish-orange	No
Concor A200	Yellowish-orange	No

As shown in table (5.7) Lipitor original and B200, the yellowish- white flocculent colour was noticed but for B201 there is no trace of hydroxpropylcellulose.

In Plavix samples, only the original sample indicated the presence of hydroxypropylcell-ulose.

Finally, Concor original and the counterfeit samples have no indication of the presence of hydroxypropylcellulose.

5.5Summary of the Results of Known Counterfeit Samples

The above analysis revealed that, the counterfeited drug has characteristics different from the genuine one. Some of the counterfeited drug has no active ingredients at all, while some others have some active ingredients significantly below the pharmacopoeial limits.

These results indicated that the (HPLC) analysis can successfully differentiate counterfeit from non-counterfeit medicines.

Further analysis of Plavix confirmed that it contains starch while the original non-counterfeited Plavix has no starch. The price of active material is many times higher than the price of starch.

This finding confirms the fact that counterfeiters usually use starch instead of active ingredients. This is a typical example of counterfeit medicine characterised by wrong active and wrong quantity or other inactive ingredients (WHO 2006 a).

CHAPTER SIX

RESULTS OF PHASE ONE (AMMAN) SURVEY TEST SAMPLES

Chapter Six

6. Results of Phase One (AMMAN) Survey Test Sample

This chapter presents the results of the analysis of phase one

6.1 Results of Testing Analysis

Following are the results of all tested samples:

6.1.1 Results of Co-Diovan Analysis

Co-Diovan was subjected to two tests:

Results of Physical Testing Physical testing of Co-Diovan included visual inspection of the package. It was found that all samples that obtained from different pharmacies have the same packaging as the original package, the font size printing, the colour of the package, the logo of the manufacturing company are all similar to the original packaging. The tablets were weighed and compared to the weight of the original, which were ranged from 306 mg to312.8 mg for each tablet. It was also noticed that all the tablets weights were found within the range, with same colour, size and shape of the original tablets.

Results of Chemical Analysis

The analysis of Co-Diovan was performed by using high performance liquid chromatography for the determination of valsartan/ hydrochlorothiazide assay as well as its

related impurities. Thirty three samples of Co-Diovan were analysed for their assay and related impurities as shown below.

All Co- Diovan samples were coded with the letter C. Table (6.1) shows the results of assay testing of Co-Diovan.

Table (6.1): Results of Assay Testing of Co-Diovan

USP acceptance limits for Co-Diovan are given in the boxes overleaf.

90 % ≤ Assay Limit ≤ 110%

Sample ID	Batch No.	Manufacture Date	Expiry Date	% Assay Valsartan	% Assay Hydrochlorothiazide
C1	S0425	7-2008	6-2011	96.8	99.5
C2	S0425	7-2008	6-2011	98.4	100.9
C3	S0390	4-2008	3-2011	96.8	100.2
C4	S0425	7-2008	6-2011	97.6	100.6
C5	S0425	7-2008	6-2011	97.2	100.3
C6	S0425	7-2008	6-2011	98.4	101.8
C7	S0425A	7-2008	6-2011	98.8	102.6
C8	S0390	4-2008	3-2011	97.7	100.4
C9	S0390	4-2008	3-2011	99.2	101.9
C10	S0425	7-2008	6-2011	98.2	101.8
C11	S0425	7-2008	6-2011	97.1	103.6
C12	S0425	7-2008	6-2011	95.7	102.5
C13	S0425	7-2008	6-2011	100.3	102.3
C14	S0425	7-2008	6-2011	95.8	103.0

Sample ID	Batch No.	Manufacture Date	Expiry Date	% Assay Valsartan	% Assay Hydrochlorothiazide
C15	S0425	7-2008	6-2011	96.6	103.0
C16	S0390	4-2008	3-2011	97.5	103.8
C17	S0425	7-2008	6-2011	96.6	102.1
C18	S0425	7-2008	6-2011	96.9	99.4
C19	S0425	7-2008	6-2011	97.0	102.3
C20	S0425	7-2008	8-2011	95.4	102.3
C21	S0295	11-2007	10-2010	96.8	103.7
C22	S0425A	7-2008	6-2011	99.4	100.7
C23	S0425	7-2008	6-2011	100.0	101.0
C24	S0313	12-2007	11-2010	100.1	101.0
C25	S0491	4-2009	3-2012	103.0	104.2
C26	S0425	7-2008	6-2011	101.7	104.4
C27	S0390	4-2008	3-2011	98.3	102.5
C28	S0313	12-2007	11-2010	102.3	105.6
C29	S0425	7-2008	8-2011	98.5	101.5
C30	S0491	4-2009	3-2012	99.2	101.2
C31	S0355	3-2008	2-2011	99.8	100.8
C32	S0390	4-2008	3-2011	97.7	102.6
C33	S0425	7-2008	8-2011	99.9	103.4

Results of Co-Diovan analysis shown in table (6.1) indicated that all samples have contents within acceptable limits ranging between 90 – 110 percent.

The only note that should be mentioned here is that batches numbers C7and C22 have been followed with a letter A. This showed a different pattern, which might indicate that when changing the batch number; the possibility of this situation being exploiting by

counterfeiters is increased. More likely, this has been a repackaging operation i.e. the single batch of drug capsules has been re-blistering packed and re-boxed for another generic distributor and hence the batch number has recognised this by the addition of an A to the end of the batch number.

Table (6.2) shows the results of related impurities for Co-Diovan.

Table (6.2): Results of Related Impurities Testing of Co-Diovan

USP acceptance limits for Co-Diovan Related Impurities are given in the boxes below.

Impurity A ≤ 1.0%

Any Impurity ≤ 0.2%

Total Impurities ≤ 1.3%

Sample ID	% Impurity A	%Related at 20 min. Retention Time	%Related at 23 min. Retention Time	%Total Impurities
C1	0.03	0.01	0.01	0.05
C2	0.03	0.01	0.01	0.05
C3	0.03	0	0.02	0.05
C4	0.03	0.02	0.03	0.08
C5	0.03	0.03	0.03	0.09
C6	0.03	0.02	0.04	0.09
C7	0.03	0.02	0.03	0.08
C8	0	0	0	0
C9	0.01	0.01	0.01	0.03
C10	0.03	0.01	0.01	0.05
C11	0.05	0.06	0.01	0.13

Sample ID	% Impurity A	%Related at 20 min. Retention Time	%Related at 23 min. Retention Time	%Total Impurities
C12	0.05	0.04	0.01	0.10
C13	0.04	0.07	0.01	0.13
C14	0.05	0.05	0.01	0.11
C15	0.05	0.05	0.01	0.11
C16	0.02	0.03	0.01	0.06
C17	0.04	0.05	0.01	0.12
C18	0.04	0.06	0.01	0.11
C19	0.05	0.07	0.01	0.13
C20	0.05	0.03	0.01	0.09
C21	0.05	0.03	0.01	0.10
C22	0.04	0.04	0.01	0.09
C23	0.04	0.05	0.01	0.10
C24	0.06	0.05	0.02	0.13
C25	0.06	0.06	0.02	0.14
C26	0.05	0.05	0.01	0.11
C27	0.04	0.03	0.02	0.09
C28	0.04	0.04	0.01	0.09
C29	0.04	0.06	0.01	0.11
C30	0.05	0.04	0.01	0.10
C31	0.04	0.05	0.01	0.10
C32	0.05	0.06	0.01	0.12
C33	0.05	0.06	0.01	0.12

Co-Diovan related impurities analyses as shown in table (6.2) indicated that all samples were shown content within acceptable limit.

Figure (6.1) shows the chromatograph for assay and related impurities for Co-Diovan.

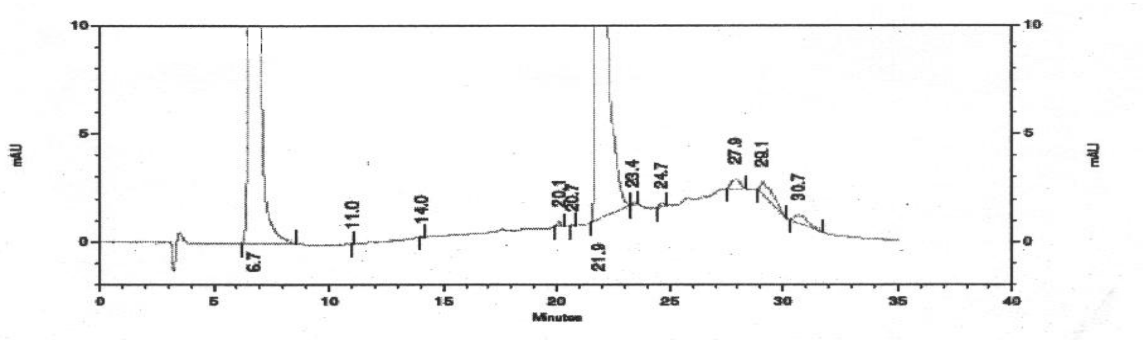

Figure (6.1): Chromatograph for Assay and Related Impurities for Co-Diovan

Results of Co-Diovan analyses indicated that no unknown peaks were observed and all samples were shown content within acceptable limits.

All samples analysed were within the pharmacopoeial limits and are considered safe pharmaceuticals.

Impurity A is for Benzothiadiazine related compound A not more than 1%, valsartan related compound A (S)-N-butyryl-N-((2-(1H-tetrazole-5-yl)-biphenyl-4-yl)-methyl1)-valine.(Ivanovic, Malenovic and Jancic 2007), the unknown impurities "any other impurity" was found less than0.2% which is the acceptable limit. The total impurities were found less than 1.3% which indicates that the related impurities analyses as shown in table (6.1) were within acceptable limits. Based on the findings it was concluded that there is no counterfeit Co-Diovan products found within these samples.

6.1.2 Results of Plavix Analysis

Plavix was subjected to two tests:

Results of Physical Testing

Physical testing of Plavix included visual inspection of the package. It was found that all samples that obtained from different pharmacies have the same packaging as the original package including the font size printing, the colour of the package, and the logo of the manufacturing company are all similar to the original packaging. The tablets were weighed and compared to the weight of the original which was ranged from (252 mg to256.9 mg) for each tablet. It was also noticed that all the tablets weights were found within the range, and have the same colour, size and shape of the original tablets.

Results of Chemical Analysis

The chemical analysis of Plavix was performed by using high performance liquid chromatography for the determination of clopidogrel assay as well as its related impurities. Thirty three samples of Plavix were analysed. All Plavix samples were coded with the letter D; the results are shown in table (6.3).

Table (6.3): Results of Assay and Related Impurities Testing of Plavix.

USP acceptance limits for Plavix are given in the boxes overleaf.

90%≤ Assay limit ≤110%.

Impurity A ≤ 1.2% Total Impurities ≤ 2.5

Impurity C ≤ 1.5%

SAMPLE ID	BATCH NO.	MANUF. DATE	EXPIRY DATE	% ASSAY	% IMPURITY A	% IMPURITY C	% TOTAL IMPURITIES
D1	2359	4-2008	4-2011	100.6	0.05	0.43	0.50
D2	2359	4-2008	4-2011	98.9	0.08	0.46	0.57
D3	2241	10-2007	10-2010	98.8	0.09	0.74	0.87
D4	2129	12-2006	12-2009	99.5	0.07	0.94	1.04
D5	2359	4-2008	4-2011	98.6	0.06	0.51	0.61
D6	2323	2-2008	2-2011	99.4	0.07	0.91	0.99
D7	2359	4-2008	4-2011	99.0	0.12	0.31	0.45
D8	2359	4-2008	4-2011	98.4	0.15	0.39	0.55
D9	2359	4-2008	4-2011	99.1	0.15	0.40	0.58
D10	2359	4-2008	4-2011	100.4	0.15	0.41	0.58
D11	2424	9-2008	9-2011	97.0	0.03	0.78	0.85
D12	2359	4-2008	4-2011	96.0	0.04	0.72	0.80
D13	2359	4-2008	4-2011	97.5	0.04	0.74	0.81
D14	2424	9-2008	9-2011	97.3	0.04	0.83	0.91
D15	2359	4-2008	4-2011	96.1	0.04	0.78	0.86
D16	2359	4-2008	4-2011	97.7	0.05	0.78	0.84
D17	2359	4-2008	4-2011	97.7	0.04	0.75	0.83
D18	2359	4-2008	4-2011	94.8	0.04	0.76	0.84
D19	2359	4-2008	4-2011	96.1	0.04	0.80	0.87
D20	2359	4-2008	4-2011	96.9	0.06	0.79	0.86

SAMPLE ID	BATCH NO.	MANUF. DATE	EXPIRY DATE	% ASSAY	% IMPURITY A	% IMPURITY C	% TOTAL IMPURITIES
D21	2424	9-2008	9-2011	96.9	0.05	0.86	0.92
D22	2241	10-2007	10-2010	96.1	0.05	1.13	1.21
D23	2490	11-2008	11-2011	102.6	0.05	0.60	0.64
D24	2490	11-2008	11-2011	102.0	0.05	0.69	0.77
D25	2359	4-2008	4-2011	101.7	0.05	0.49	0.54
D26	2424	9-2008	9-2011	103.4	0.03	0.35	0.39
D27	2241	10-2007	10-2010	102.6	0.01	0.49	0.50
D28	2273	1-2008	1-2011	99.4	0.04	0.92	0.99
D29	2490	11-2008	11-2011	99.7	0.02	0.54	0.67
D30	2490	11-2008	11-2011	101.7	0.03	0.63	0.69
D31	2424	9-2008	9-2011	102.0	0.02	0.41	0.43
D32	2490	11-2008	11-2011	102.6	0.04	0.36	0.40
D33	2359	4-2008	4-2011	101.7	0	0.41	0.41

Plavix assay and related impurities analysis as shown in table (6.3) which indicated that the typical content of active pharmaceutical ingredients (API) was between (96.0-103.4%) while the acceptable limits ranging from 90-110%. This means that all samples analysed were within the pharmacopoeial limits and are considered safe pharmaceuticals. As for the related impurities, clopidogrel related impurity A is ((S)-(ochlorophenyl)-6, 7-dihydrothieno[3,2-c] pyridine5(4H)-acetic acid, Hydrochloride was found less than 1.2% which is within the acceptable limits and related impurities a chiral isomer of clopidogrel named as clopidogrel related compound C is (-)-R-(ochlorophenyl)-6,7-dihydrodtheino [3,2-c] pyridine-5(4H)- acetate, hydrogen sulphate (Mohan *et al.* 2008). Was found less than 1.5%.

While total impurities were found less than 2.5% which indicates that the related impurities analyses as shown in table (6.3) were within acceptable limits. Based on these findings it was concluded that there is no counterfeit Plavix products found in these samples.

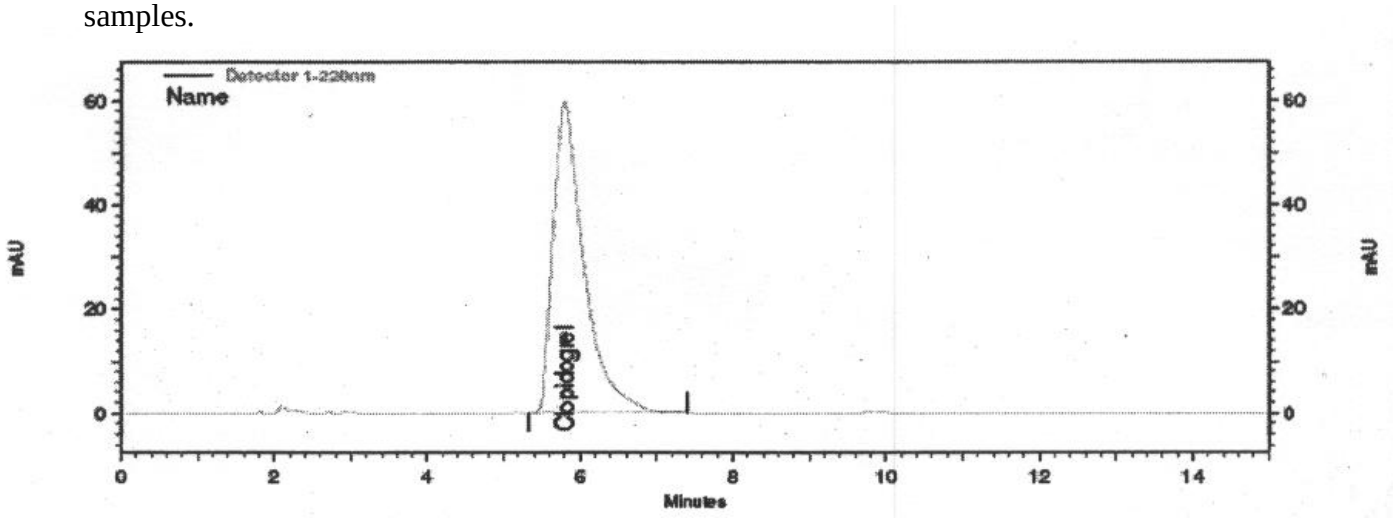

Figure (6.2): Chromatograph for Plavix Assay.

Figure (6.2) shows the chromatograph for Plavix assay. It shows that the retention time and the UV-absorption spectrum shown in figure 6.2 indicated that the sample is Plavix and no unknown peaks were observed.

Figure (6.3) shows the chromatograph for related impurities of Plavix.

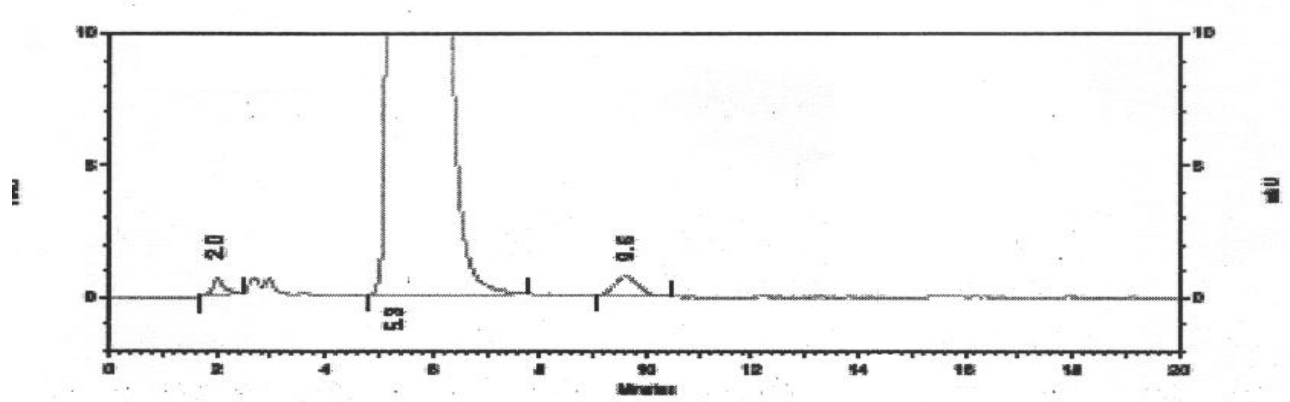

Figure (6.3): Chromatograph for Related Impurities for Plavix

6.1.3 Results of Concor Analysis

Concor was subjected to two tests:

Results of Physical Testing

Physical testing of Concor included visual inspection of the package. It was found that all samples that obtained from different pharmacies from (Amman, Irbid and Zarqa) have the same packaging as the original sample, and the font size printing, the colour of the package, and the logo of the manufacturing company are all similar to the original packaging. The tablets were weighted and compared to the weight of the original which was ranged from 171 mg to 173.9 mg for each tablet. It was also noticed that all the tablets weights were found within the range, the colour, size and shape of the original.

Results of Chemical Analysis

The chemical analysis of Concor was performed by using high performance liquid chromatography for the determination of bisoprolol assay as well as its related impurities. Thirty three samples of Concor were analysed. All Concor samples were coded with the letter A; the results are shown in table (6.4).

Table (6.4): Results of Assay and Related Impurities Testing of Concor

USP acceptance limits for Concor are given in the boxes below.

90%≤ Assay limit ≤110%.

Max. Impurity ≤0.25%

Total Impurities ≤ 1.0%

Sample ID	Batch No	Manu. Date	Expiry Date	%Assay	%Max. Impurity	%Total Impurities
A1	5787901	8-2008	7-2011	97.4	0.04	0.16
A2	5787901	8-2008	7-2011	96.5	0.04	0.16
A3	5508101	11-2007	10-2010	97.5	0.07	0.26
A4	5707301	6-2008	5-2011	99.1	0.04	0.16
A5	5788501	8-2008	7-2011	98.9	0.07	0.13
A6	5787901	8-2008	7-2011	98.0	0.06	0.20
A7	5787901	8-2008	7-2011	98.2	0.07	0.13
A8	5787901	8-2008	7-2011	99.6	0.06	0.15
A9	5787901	8-2008	7-2011	100.4	0.07	0.18
A10	5787901	8-2008	7-2011	101.0	0.07	0.16
A11	100536	11-2008	10-2011	100.2	0.05	0.17
A12	100536	11-2008	10-2011	97.9	0.05	0.17
A13	5787901	8-2008	7-2011	98.4	0.05	0.20
A14	5787901	8-2008	7-2011	98.2	0.05	0.13
A15	100536	11-2008	10-2011	98.8	0.05	0.08
A16	100536	11-2008	10-2011	97.7	0.04	0.12

Sample ID	Batch No	Manu. Date	Expiry Date	%Assay	%Max. Impurity	%Total Impurities
A17	101071	2-2009	1-2012	101.3	0.03	0.13
A18	100536	11-2008	10-2011	98.5	0.05	0.09
A19	101071	2-2009	1-2012	99.7	0.05	0.16
A20	101071	2-2009	1-2012	99.5	0.03	0.11
A21	5508101	11-2007	10-2010	102.7	0.05	0.19
A22	101071	2-2009	1-2012	97.6	0.05	0.17
A23	5507403	11-2007	10-2010	96.6	0.08	0.27
A24	101071	2-2009	1-2012	97.9	0.09	0.25
A25	101071	2-2009	1-2012	98.4	0.09	0.28
A26	101759	5-2009	2-2012	98.2	0.08	0.24
A27	101071	2-2009	1-2012	97.5	0.06	0.18
A28	101071	2-2009	1-2012	97.4	0.08	0.16
A29	101071	2-2009	1-2012	97.2	0.04	0.12
A30	101071	2-2009	1-2012	97.2	0.05	0.13
A31	101071	2-2009	1-2012	97.8	0.05	0.13
A32	5787901	8-2008	7-2011	96.6	0.08	0.29
A33	101071	2-2009	1-2012	99.3	0.05	0.17

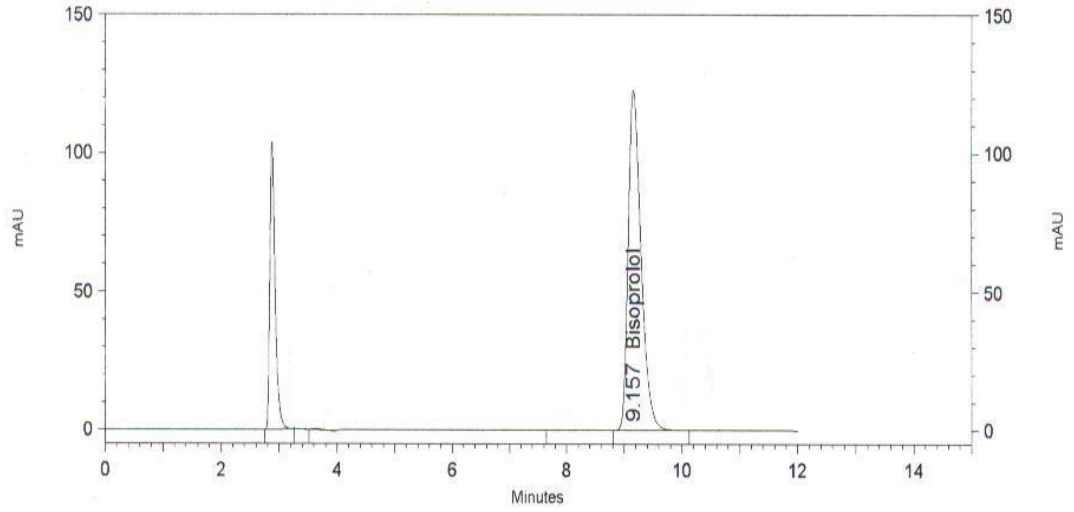

Figure (6.4): Chromatograph of Assay for Concor

Figure (6.4) shows chromatograph of assay for Concor. It shows that the retention time

The UV-absorption spectrum shown in Figure 6.4 indicated that the sample is Concor, the first peak is for fumaric acid and the second peak is bisoprolol which is the active ingredient in Concor and no unknown peaks were observed.

Figure (6.5) shows the chromatograph for related impurities of Concor. The related impurities for concor are Bisoprolol Dibenzylether, Bisoprolol n-propoxy-isomer, Bisoprolol derivative Diphenylmethane, Bisoprolol Benzylalcohol and Bisoprolol derivative Z/E-olefin (USP 2006).

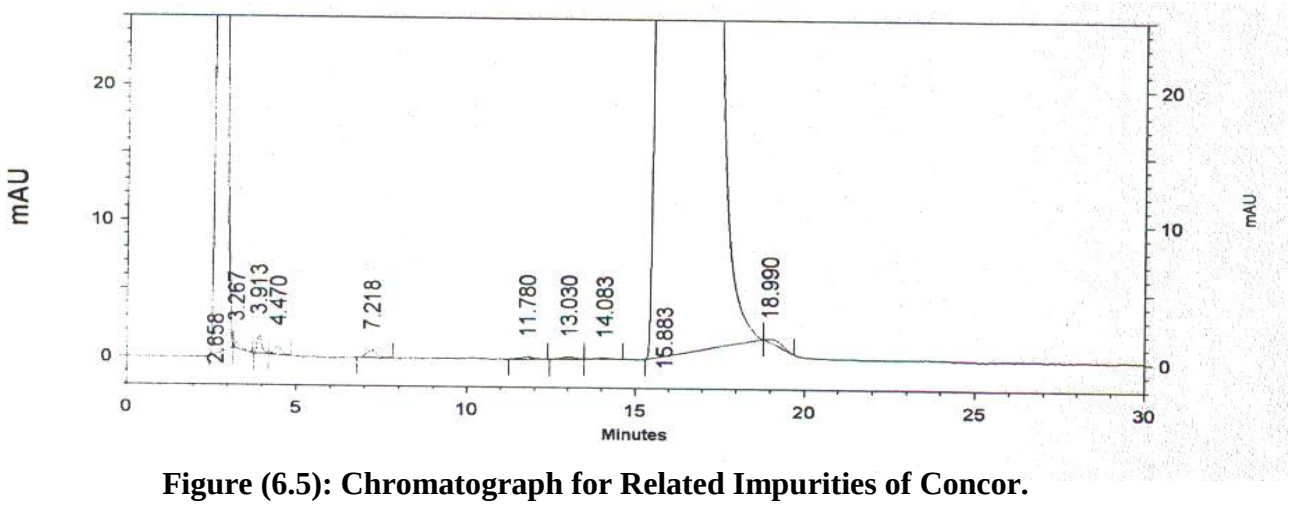

Figure (6.5): Chromatograph for Related Impurities of Concor.

Results of Concor analyses indicated that all samples were shown to have content within acceptable limits.

6.1.4 Results of Lipitor Analysis

Lipitor was subjected to three tests:

Results of Physical Testing

Physical testing of Lipitor included visual inspection of the package. It was found that all samples that obtained from different pharmacies look exactly as the original package, and the font size printing, the colour of the package, and the logo of the manufacturing company are all similar to the original packaging. The tablets were weighed and compared to the weight of the originals and found to range between 303 mg to 318 mg for each tablet, which is same as original. It was also noticed that all the tablets colour, size and shape are same as that of the originals.

Results of Chemical Analysis : chemical testing of Lipitor was comprised of two analyses.

HPLC Analysis: The analysis of Lipitor is performed by using high performance liquid chromatography for the determination of active ingredient in the product (atorvastatin)

Thirty three samples of Lipitor were analysed for their assay and related impurities. All Lipitor samples were coded with the letter B; the results are shown in table (6.5).

Table (6.5): Results of Assay and Related Impurities Testing of Lipitor (20mg)

USP acceptance limits for Lipitor are given in the boxes below.

90%≤ Assay limit ≤110%.

Max. Imp. ≤ 1.5%

Total Imp ≤ 3.5%

SAMPLE ID	BATCH NO.	MANUF. DATE	EXPIRY DATE	% ASSAY	% MAX. IMPURITY	% TOTAL IMPURITIES
B1	0630107	10-2007	9-2010	98.4	0.15	0.37
B2	0649077	7-2007	6-2010	97.9	0.09	0.44
B3	0270077	7-2007	6-2010	97.5	0.10	0.47
B4	007057	5-2007	4-2010	97.4	0.16	0.44
B5	0649077	7-2007	6-2010	98.9	0.11	0.35
B6	0630107	10-2007	9-2010	97.8	0.10	0.31
B7	0270077	7-2007	6-2010	99.2	0.12	0.36
B8	0630107	10-2007	9-2010	97.3	0.14	0.39
B9	0630107	10-2007	9-2010	98.5	0.15	0.37
B10	0630107	10-2007	9-2010	98.1	0.15	0.39

SMPLE ID	BATCH NO.	MANUF. DATE	EXPIRY DATE	% ASSAY	.% MAX MIMPURITY	% TOTAL IMPURITIES
B11	0630107	10-2007	9-2010	97.3	0.13	0.37
B12	0270077	7-2007	6-2010	100.4	0.18	0.71
B13	0630107	10-2007	9-2010	97.9	0.18	0.65
B14	0049107	10-2007	9-2010	99.0	0.16	0.57
B15	0649077	7-2007	6-2010	97.0	0.21	0.74
B16	0649077	7-2007	6-2010	98.7	0.23	0.77
B17	0630107	10-2007	9-2010	97.5	0.15	0.66
B18	0630107	10-2007	9-2010	96.3	0.18	0.72
B19	0330088	3-2008	2-2011	99.1	0.21	0.57
B20	0330088	3-2008	2-2011	99.1	0.26	0.65
B21	0649077	7-2007	6-2010	98.9	0.25	0.84
B22	0049107	10-2007	9-2010	98.9	0.28	0.76
B23	0630107	10-2007	9-2010	97.6	0.07	0.37
B25	0649077	7-2007	6-2010	96.9	0.09	0.47
B26	0330038	3-2008	2-2011	99.0	0.11	0.40
B27	0330038	3-2008	2-2011	97.2	0.16	0.44
B28	0270077	7-2007	6-2010	98.5	0.23	0.62
B29	0630107	10-2007	9-2010	97.1	0.11	0.33
B30	0330038	3-2008	2-2011	99.3	0.20	0.42
B31	0630107	10-2007	9-2010	97.3	0.22	0.45
B32	0649077	7-2007	6-2010	99.2	0.24	0.45

SMPLE ID	BATCH NO.	MANUF. DATE	EXPIRY DATE	% ASSAY	.% MAX MIMPURITY	% TOTAL IMPURITIES
B33	0330038	3-2008	2-2011	98.9	0.34	0.51

Results, as shown in table (6.5), indicated that the typical content of active pharmaceutical ingredients (API) were between 96.3-100.4% while the acceptable limits ranging from 90-110%. This means that all samples analysed were within the pharmacopoeial limits and are considered safe pharmaceuticals. The related impurities in Lipitor are: Atorvastatin amide, Desfluoro Atorvastatin, Diastereoisomer, O-methyl Atorvastatin, Atorvastatin lactone and Atorvastatin methyl ester (Monar, Damic and Nigovic 2010). The maximum impurity was found to be less than 1.5% which is within the acceptable limits. Total impurities were found less than 3.5% which indicates that the related impurities analysis as shown in table (6.5) was within acceptable limits. Based on the findings it was concluded that there are no counterfeit Lipitor products found within these samples.

Figure (6.6) shows the chromatographic profile of Lipitor for assay.

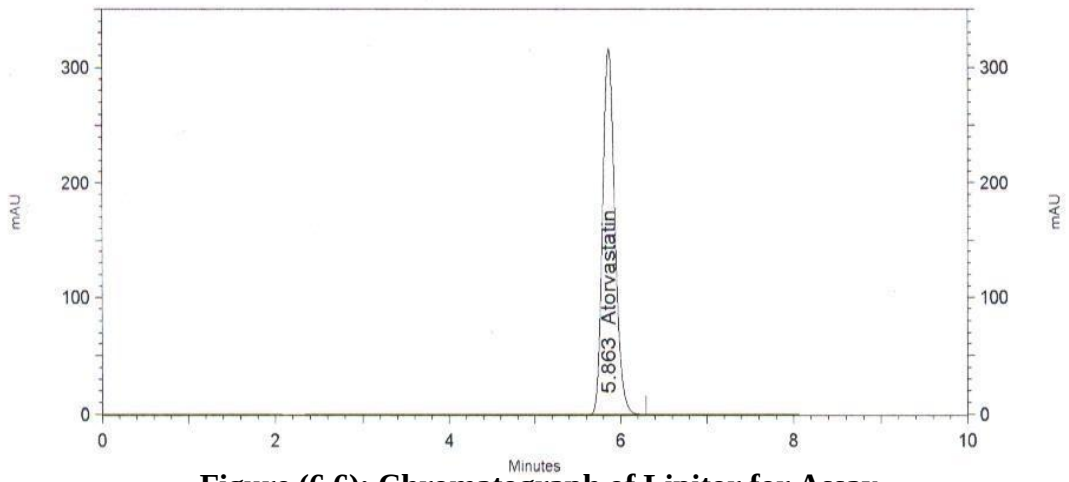

Figure (6.6): Chromatograph of Lipitor for Assay

Chromatographic profile of samples of Lipitor indicated that the retention time and the UV-absorption spectrum shown in figure 6.6 indicated that the sample is Lipitor and no unknown peaks were observed.

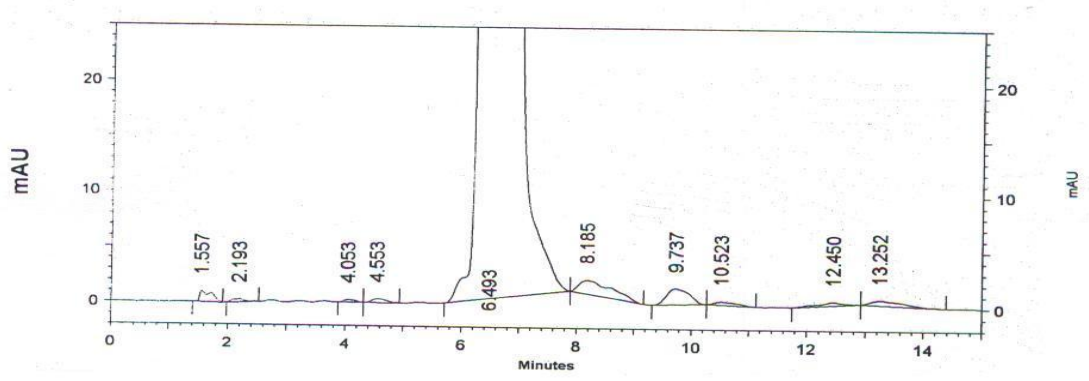

Figure (6.7): Chromatograph for Related Impurities of Lipitor

Figure (6.7) shows the related impurities of Lipitor, after calculations they were found within pharmacopoeial limits.

Results of Dissolution Analysis

In order to evaluate the formulation effectiveness, dissolution was performed on Lipitor since atorvastatin is poorly soluble and special care with formulation and manufacturing parameters is a must to insure atorvastatin tablets compliance to the required standards of solubility.

All thirty-three samples were analysed for their drug release and the results are presented in table (6.6), which indicates that all samples were released within the limits included in the pharmacopoeia.

Table (6.6): Results of Dissolution Testing of Lipitor (20mg)

% Drug Release Limit ≥ %80

Sample Code	Batch No.	Manufacture Date	Expiry Date	% Release in 60 minutes
B1	0630107	10-2007	9-2010	99.4
B2	0649077	7-2007	6-2010	101.7
B3	0270077	7-2007	6-2010	102.1
B4	007057	5-2007	4-2010	101.6
B5	0649077	7-2007	6-2010	101.9
B6	0630107	10-2007	9-2010	101.4
B7	0270077	7-2007	6-2010	101.2
B8	0630107	10-2007	9-2010	99.7
B9	0630107	10-2007	9-2010	100.7
B10	0630107	10-2007	9-2010	98.9
B11	0630107	10-2007	9-2010	99.0
B12	0270077	7-2007	6-2010	98.8
B13	0630107	10-2007	9-2010	98.8
B14	0049107	10-2007	9-2010	98.8
B15	0649077	7-2007	6-2010	100.3
B16	0649077	7-2007	6-2010	101.0
B17	0630107	10-2007	9-2010	100.6
B18	0630107	10-2007	9-2010	101.5
B19	0330038	3-2008	2-2011	102.3
B20	0330038	3-2008	2-2011	101.6
B21	0649077	7-2007	6-2010	101.2
B22	0049107	10-2007	9-2010	100.8
B23	0630107	10-2007	9-2010	101.2
B24	0649077	7-2007	6-2010	101.4
B25	0649077	7-2007	6-2010	101.8

Sample Code	Batch No.	Manufacture Date	Expiry Date	% Release in 60 minutes
B26	0330038	3-2008	2-2011	101.1
B27	0330038	3-2008	2-2011	100.7
B28	0270077	7-2007	6-2010	101.7
B29	0630107	10-2007	9-2010	101.2
B30	0330038	3-2008	2-2011	100.7
B31	0630107	10-2007	9-2010	99.5
B32	0649077	7-2007	6-2010	98.9
B33	0330038	3-2008	2-2011	99.2

Results of the dissolution analysis for the thirty-three samples as shown in table (6.6) showed that the percentage of the drug release for the drug was found between 98.8- 102.3 while the acceptable percentage limit of drug release, according the United States Pharmacopoeia was 80% or over. These results confirm that these samples were produced within the pharmacopoeial standards and were considered safe medicine.

CHAPTER SEVEN

RESULTS OF PHASE TWO (JORDAN) SURVEY TEST SAMPLE

Chapter Seven

Results of Phase Two (Jordan) Survey Test Sample

Results of the analysis of stage one indicated that no counterfeited drug was found.

Based on the results of the first phase of the analysis which included only samples from Amman, the capital of Jordan, further analysis was needed and more cities were included to have a better comprehension of the problem of counterfeit pharmaceuticals. Therefore, it has been decided that one of the four drugs will be analysed in the second stage**.** For this stage, Concor (bisoprolol fumarate) was chosen after discussion with (JFDA) officials who have indicated that counterfeited Concor has been found recently in the Jordanian market, which was seemingly smuggled from a neighboring country.

To determine the genuine medicine from the counterfeit one, the physical appearance and the chemical results were used as the quality indicators.

7.1 Results of Analysis of Concor

Concor was subjected to two tests:

7.1.1 Results of Physical Testing

Physical testing of Concor included visual inspection of the package. It was found that the counterfeit packaging looks exactly as the original package, the font size printing, the colour of the package, the logo of the manufacturing company are all similar to the original packaging. The tablets were weighed and compared to the weight of the original which was

ranged from 171 mg to173.9 mg for each tablet. It was also noticed that all the tablets weights were found within the range, the colour, size and shape of the original.

7.1.2 Results of Chemical Analysis

The chemical analysis of Concor is performed by using high performance liquid chromatography for determination of bisoprolol assay as well as its related impurities. Tests included the use of pharmacopoeial method of high performance liquid chromatography (HPLC) for all samples. 40 Samples of Concor were analysed to confirm the amount of the active ingredients. All Concor samples were coded with the letter A. Results are shown in table (7.1).

Table (7.1): Results of Assay and Related Impurities Testing of Concor

USP acceptance limits for Concor are given in the boxes below.

90%≤ Assay limit ≤110%.

Max. Impurity ≤0.25%

Total Impurities ≤ 1.0

Sample ID.	Batch No.	Manufacturing Date	Expiration Date	% Assay	% Max. Impurity	% Total Impurities
A 34	103219	6-2009	5-2012	101.7	0.17	0.20
A 35	101759	3-2009	2-2012	100.8	0.03	0.06
A 36	103219	6-2009	5-2012	101.7	0.03	0.06
A 37	101759	3-2009	2-2012	101.2	0.14	0.17
A 38	102529	3-2009	2-2012	98.0	0.13	0.16
A 39	101759	3-2009	2-2012	100.6	0.13	0.15
A 40	101759	3-2009	2-2012	100.8	0.13	0.15

Sample ID.	Batch No.	Manufacturing Date	Expiration Date	% Assay	% Max. Impurity	% Total Impurities
A 41	103219	6-2009	5-2012	100.7	0.11	0.12
A 42	101759	3-2009	2-2012	98.4	0.05	0.07
A 43	102530	3-2009	2-2012	98.9	0.05	0.05
A 44	101759	3-2009	2-2012	99.9	0.05	0.07
A 45	103219	6-2009	5-2012	101.4	0.03	0.04
A 46	103219	6-2009	5-2012	100.6	0.04	0.05
A 47	103219	6-2009	5-2012	98.8	0.09	0.27
A 48	101759	3-2009	2-2012	99.8	0.09	0.20
A 49	103219	6-2009	5-2012	100.7	0.09	0.31
A 50	103219	6-2009	5-2012	100.9	0.09	0.31
A 51	5787901	8-2008	7-2011	100.6	0.07	0.20
A 52	101759	3-2009	2-2012	99.8	0.06	0.18
A 53	102529	3-2009	2-2012	99.7	0.04	0.14
A 54	102530	3-2009	2-2012	98.6	0.06	0.24
A 55	103219	6-2009	5-2012	100.9	0.09	0.21
A 56	103219	6-2009	5-2012	99.5	0.10	0.23
A 57	102529	3-2009	2-2012	99.9	0.05	0.19
A 58	103219	6-2009	5-2012	98.8	0.06	0.18
A 59	103219	6-2009	5-2012	99.3	0.06	0.19
A 60	101759	3-2009	2-2012	98.7	0.07	0.27
A 61	104103	7-2009	6-2012	99.0	0.08	0.29
A 62	102529	3-2009	3-2012	98.7	0.07	0.25

Sample ID.	Batch No.	Manufacturing Date	Expiration Date	% Assay	% Max. Impurity	% Total Impurities
A 63	103219	5-2009	5-2012	100.0	0.05	0.16
A 64	101759	3-2009	5-2012	98.3	0.07	0.27
A 65	102529	3-2009	2-2012	101.9	0.05	0.14
A 66	103219	6-2009	5-2012	99.7	0.09	0.29
A 67	103219	6-2009	5-2012	100.2	0.10	0.30
A 68	101759	3-2009	2-2012	100.8	0.09	0.27
A 69	103219	6-2009	5-2012	101.1	0.09	0.27
A 70	102529	3-2009	2-2012	98.4	0.07	0.29
A 71	101759	3-2009	2-2012	99.0	0.04	0.11
A 72	104103	7-2009	6-2012	101.4	0.08	0.26
A 73	103219	6-2009	5-2012	99.6	0.09	0.28

Seventy three samples of Concor were analysed , thirty three for stage one and forty for stage two as shown in tables (6.2) and (7.1)which indicated that the typical content of active pharmaceutical ingredients (API) was between 96.5-102.7% while the acceptable limits ranging from 90-110%. This means that all samples analysed were within the pharmacopoeial limits and are considered safe. As for the related impurities, the maximum impurity was less than 0.25% which is within the acceptable limit. The total impurities were found less than 1.0% which indicates that the related impurities analyses were within acceptable limits. Based on these findings it was concluded that there is no counterfeit Concor products found in these samples.

CHAPTER EIGHT

DISCUSSIONS

Chapter Eight

8. Discussions

This research objective was to determine the extent to which counterfeit pharmaceutical products available in Jordan. To reach this end four life saving pharmaceutical were used for HPLC testing.

In this study, the reason behind selecting these samples of life saving medications was that, counterfeiters have frequently targeted these pharmaceuticals in the past due to their high prices and high demand which made these products attractive targets to counterfeiters according to JFDA officials. Moreover WHO stated that life saving medications globally are targeted by counterfeiters due to same reasons (WHO 2006).

All samples were physically and chemically tested according to the relevant pharmacopoeia using high performance liquid chromatography. Dissolution testing was performed for Lipitor only in order to evaluate the formulation effectiveness; since atorvastatin is poorly soluble and special care with formulation and manufacturing parameters is a must to ensure atorvastatin tablets compliance to the required standards of solubility.

All samples were checked for their active ingredients and their related impurities. Impurities are unwanted chemicals that remain with the active could be associated with it or created during formulation of the product or could be generated at any synthetic steps or upon aging of both active. Therefore, the process of controlling the impurities is considered as an important issue in order to ensure the safety, efficacy and have an impact on the stability of pharmaceutical products. That is why pharmacopoeia has an essential role in regulating this process by identifying specification limits.

Results of in the study sample. While these results do not necessarily indicate that there are no counterfeit pharmaceuticals in the country but it is quite an interesting result to know that the country campaign against counterfeit trade seems to be successful in targeting such a trade in four very important life-saving pharmaceuticals.

Obviously, these results did not indicate that there are no counterfeit pharmaceuticals in the country as a whole. Counterfeiters tend to move their activity of manufacturing of certain types of counterfeit medicines to other products once they realise that the products they manufacture are being subjected to further emphasis by authorities.

As reported earlier, the quality of the four sampled pharmaceuticals used in this study was found to comply with the USP quality standard. The explanation for these results is that the health authorities' campaigns against counterfeit drugs have been successful. These results confirm the efficiency of the new regulations that JFDA has implemented in 2008, and the effective implementation of new strict public health laws which include tougher penalties and more effective enforcement measures.

The establishment and implementation of the "2008 new public health" laws that complies with modern international treaties seems to have had an effect of at least significantly reducing counterfeit pharmaceutical levels in the country. Jordan initiated a TRIPS (Agreement on Trade-Related Aspects of Intellectual Property Rights) implementation reform which aimed at placing Jordan in compliance with the world trade organisation legislation. The link between counterfeiting and IP is that, trademark law protects against the unauthorised use of a product's name or its appearance in a manner which is similar to that used by the legitimate owner. Counterfeiting usually occurs when the counterfeited product appears to be made by the authentic manufacturer, even upon close inspection.

Therefore intellectual property protection may be used as a tool to help build a useful policy to help prevent counterfeiting. Since an unauthorised use of a name or appearance of a product in a way which is confusingly similar to that used by the original owner is forbidden by intellectual protection laws. Trademark owners can legally sue any party, who may produce, sell or distribute counterfeited pharmaceuticals for infringement of their trade marks (Falbalrn *et al*. 2007).

After results of phase one indicated that there was no evidence of the existence of counterfeit pharmaceuticals in, the researcher decided that further investigation of such a conclusion must be conducted in order to provide more validation to these results.

To reach this end, the researcher started a round of meetings and discussions with JFDA officials and professionals with the aim of identifying a pharmaceutical product that might have more tendencies to be targeted by counterfeiters due to some special features, such as frequency of usage. As a result of this campaign, Concor was identified as the product that should be further investigated.

To do this successfully, the researcher decided to collect samples of Concor from the three largest cities in Jordan.

High Performance Liquid Chromatography (HPLC) tests were performed and results confirmed phase one results, no counterfeit products were found.

These results provided more assurances that governmental measures in Jordan to counter this trade were successful.

Another important factor working for the results of this research is the level of sophistication of the technology used in the analysis. This technology is owned and operated by a very well-known pharmaceutical manufacturer in Jordan "Jordanian

Pharmaceutical Manufacturing Co. PLC" which operates state of the art pharmaceutical manufacturing facilities which were made accessible for the researcher to use with no limitations what so ever.

Another contributing factor to the success of this research was the use of HPLC as a quantitative testing method which has proven to be reliable and able to accurately quantify the active ingredients present in the pharmaceutical preparations, as discussed earlier in this research.

The major advantage of HPLC is that it is a sensitive, accurate and precise method of analysis. It allows a complex analysis to be done in reasonable period of time and can accomplish the separation of components in a more complete manner (Ho and Lin 1996).

HPLC is considered widely as a stability indicating method which selectively separates each active ingredient from its degradation products and in addition separates it from its process impurities and formulation excipients (Ho and Lin 1996)

Therefore this testing method has a qualitative as well as quantitative nature. It also has the ability to detect the related impurities in the product

Despite these advantages, there are some limitations of this method. This method can detect the inadequacy or absence of active ingredient but cannot detect correct active ingredients present in correct dosage form but manufactured by illicit laboratory or manufacturer (Fraud counterfeits).

Therefore, results of testing using HPLC seemed adequate to increase the level of confidence in the results.

The researcher has validated the ability of HPLC to discriminate between counterfeited and non- counterfeit products by applying HPLC testing to samples of known counterfeit

products obtained by authorities as described earlier in the results in known counterfeit chapter. These results confirmed that samples were actually counterfeited.

This testing has provided the researcher with more confidence in the ability of HPLC as an analysis method.

However, in order to increase the level of confidence in the results of the analysis, the researcher has decided to apply more tests. Therefore, Infrared spectrometer (IR Spectrometer) was used for the identification of the existence of active ingredients in the samples. All batches of the sampled pharmaceuticals were subjected to the analysis of Infrared Spectroscopy (IR Spectroscopy).

IR spectroscopy involved collecting absorption information and analysing it in the form of an IR spectrum, followed by a comparison with a reference spectrum. Results of this testing showed that all of the study samples contained the required active ingredients, which confirms the results obtained using HPLC method.

In an attempt to identify the composition of the counterfeit samples, further analysis of the ingredients was performed such as identification of starch, lactose and hydroxypro-pylcellulose.

The above analysis revealed that, a counterfeit drug has characteristics different from the genuine one. Some counterfeited drug has no active ingredients at all, while some others have some active ingredients significantly below the USP specified limits.

These results indicated that the (HPLC) analysis could successfully differentiate counterfeit from non-counterfeit medicines.

CHAPTER NINE

CONCLUSION AND RECOMMENDATIONS

Chapter Nine

9. Conclusion and Recommendations

The main objective of this study was to determine whether there are counterfeit pharmaceuticals exist in the Jordanian market or not. To reach this end the study has examined 172 samples, which were collected during the period from March 2009 to February 2010 from the three most populated cities in the country namely, Amman (capital of Jordan), Zarqa and Irbid.

The study examined 33 samples of co-Diovan (valsartan, hydrochlorothiazide) used for treatment of high blood pressure, 33 samples of Lipitor (atorvastatin-calcium) used for cholesterol lowering, 33 samples of Plavix (clopidogrel) used for preventing blood clots in arteries, and 73 samples of Concor (bisoprolol fumarate) used for reducing high blood pressure in patients.

All samples were physically and chemically tested according to compendial requirements using high performance liquid chromatography and dissolution testing was performed for Lipitor only.

Results of all tests done in this study have not been able to detect any presence of counterfeit pharmaceuticals in the study sample. While these results do not necessarily indicate that there are no counterfeit pharmaceuticals in the country but it is quite an interesting result to know that the country campaign against counterfeit trade seems to be successful in targeting such a trade in four very important life-saving pharmaceuticals.

This conclusion is conservatively stated here due to the fact that the study survey was limited to the samples subjected to analysis which in fact indicate that such a conclusion cannot be generalised to reflect the nature of the problem of counterfeit pharmaceutical in Jordan.

Obviously, these results did not indicate that there are no counterfeit pharmaceuticals in the country as a whole. Counterfeiters tend to move their activity of manufacturing of certain types of counterfeit medicines to other products once they realise that the products they manufacture are being subjected to further emphasis by authorities.

As reported earlier, the quality of the four sampled pharmaceuticals used in this study was found to comply with the USP quality standard. The one feasible explanation for these results is that the health authorities' campaigns against counterfeit drugs have been successful. These results confirm the efficiency of the new regulations that JFDA has implemented in 2008, and the effective implementation of new strict public health laws, which include tougher penalties and more effective enforcement measures.

The main conclusion, however that can be derived from the results of this study is that, no indication of the presence of counterfeit pharmaceuticals in the sampled products used in the study in the Jordanian market given the limitations of the resources and budget made available for the conduct of this study. This study used an organised design to detect if counterfeit elements are present in the study samples. A validity test was employed in order to assure that the study is really designed in a way that permits reaching reliable results. This test used known counterfeit samples which, when subjected to exactly the same testing procedures and results, indicated that counterfeited components of the sample were correctly identified.

This study is considered as the first comprehensive research to evaluate the presence of counterfeit pharmaceutical products in Jordan. One of the major problems faced by the researcher was the absence of serious previous literature on this topic in Jordan and the Middle East.

Since 2008, Jordan has been engaging in an anti-counterfeit campaign in terms of increased legal measures, tough penalties, and increased inspection. Drug regulations have also been upgraded and several strategies were implemented as means to combat counterfeit drugs.

Global awareness in the battle against counterfeit pharmaceuticals is also increasing, the World Health Organisation (WHO) fact sheet (WHO 2003) on counterfeit medicines refer to them as 'an enormous public health challenge'.

Predictions are that pharmaceutical counterfeiting will undergo a more than 90% increase in their sales by the year 2010 (WHO 2006).

Despite this global trend, Jordan has recognised the size of the problem and has made some degree of progress in dealing with it through applying stronger regulations. However there remains much work to be done to maintain the safe and secure supply of quality of pharmaceuticals in Jordan.

Prior to the year 2008, it was noticed that during the period from 2005 to early 2008 there was a noticeable presence of counterfeit pharmaceuticals in the Jordanian market but since the implementation of the new regulations this problem is significantly reduced.

This study suggests that due to the implementation of new strict regulatory measures with harder penalties than before, the quality of pharmaceuticals has improved to the point that it was hard to find counterfeit pharmaceuticals in the market compared to the past.

The Jordanian Food and Drug Administration (JFDA) have conducted workshops for the Judiciary. Judges and law officers from twelve district of Jordan have participated in the workshops. Workshops included the following dimensions:

1. The definition of counterfeit pharmaceuticals and what really constitutes counterfeit pharmaceuticals and how they affect public health.
2. The differentiating factor between smuggled and counterfeit pharmaceutical. It is worth mentioning here that the public perception is that, it is acceptable to use smuggled products because they think it is as good as any other original products.

Workshops have emphasised the fact that, smuggled drugs actually are different from other smuggled goods such as clothes for example. Smuggled drugs sometimes contain no active ingredients, or contain the wrong ingredients, less than the therapeutic levels of the active ingredients and finally they might contain toxic ingredients, therefore they constitute a health hazard.

3. Participants were informed that Jordan has been struggling for years to protect brand names through its judiciary system, and recently they enacted more than 30 laws to combat piracy and establish an ongoing training program for judges and judiciary employees to comply with national and international legislation against piracy and counterfeit (Al- Iryani and Ba-swaid 2009).
4. One of the main objectives of this workshop was to Judges who are involved in the prosecution of counterfeiters, information about counterfeit pharmaceuticals, and the importance of implementing severe penalties for individuals or firms who might engage with this trade.

One important conclusion as a result of this workshop, a decision was taken that only well informed and well trained judges will be assigned for the prosecution of counterfeiting cases.

9.1 Recommendations

The researcher recommends the following in order to re-enforce governmental accomplishments in the area of controlling the quality of pharmaceuticals in the country:

1. In Jordan, life-saving pharmaceuticals as well as antibiotics, and almost all medications can usually be bought over the counter without prescription. Prescription is required only for sedatives, tranquilisers and narcotics. Pharmaceuticals used in this study are usually available over the counter without prescription. Therefore the researcher would recommend that dispensing of pharmaceuticals upon prescription should be strictly regulated which would be expected the possibility of selling counterfeit pharmaceuticals.
2. It is also recommended that an extra emphasis should be given to the process of vigorous testing of the quality of imported pharmaceuticals and the routine testing of new supplies in order to insure compliance with GMP.
3. As part of the health authorities' campaign against illegal dealing with pharmaceutical products, the level of awareness of physicians and pharmacists should be enhanced. When they are confronted with ineffectiveness of a commonly effective therapy, they should wonder about the quality and origin of the medicine. All parties concerned must know that counterfeit drugs are dangerous and sometimes life threatening.

4. Continuing education of consumers and health professionals about the dangers of counterfeit pharmaceuticals should be considered as a way of life. They should be encouraged to report any changes regarding the color, shape, size and any other differences in pharmaceuticals' attributes and characteristics. It has been noticed that in many cases, patients regularly discover that the pharmaceuticals that they are using are not the same as they have been familiar with, and report that to their physicians.
5. The quality of all pharmaceuticals circulating in the distribution chain should continuously be monitored by sampling and analysing them on a regular basis to ensure that the quality and safety of pharmaceuticals are assured.
6. It is also important to address the issue of cooperation among various government organisations, health workers, industry, and wholesalers. An integrative network of cooperation among these parties is assumed to be critical to maintain the integrity and security of Jordan pharmaceuticals.
7. It was reported that most confiscated pharmaceuticals came from neighboring countries. Therefore, sharing of information and cooperation with neighboring countries should be encouraged in order to stop the smuggling of counterfeit pharmaceuticals.
8. The regulatory authorities should ensure that pharmacists, hospitals, and clinics must obtain their pharmaceuticals from known sources such as a major wholesaler.
9. In Jordan, internet purchases are not a wide spread practice yet. Actually buying pharmaceuticals from the internet is very limited unlike other goods. But such a practice might suddenly be realised. Therefore, authorities must take a proactive approach in dealing with such an issue in the future.

10. Finally, it is recommended that regulatory authorities should develop an information system network to ensure effective reporting of counterfeit pharmaceuticals and any illegal activities.

REFRENCES

References

- Abdo-Rabbo, A. Bassili, A. Atta, H. (2005) 'The Quality of anti-malarials available in Yemen.' *Malaria Journal* [online]4, (28) available from <http://www.malariajournal.com/content/4/1/2> [24 February 2009]

- Aka, E. Legris C, Tsuyoshi T, Matsushita R and Kimura K.(2005) 'Counterfeit medicine detection by authenticity investigation a Pilot study in the street market of *Cote d' Ivoire*.'*Japanese Journal of Social Pharmacy* 24,(2) 7-16.Available from <http://www.sciencelinks.jp/j-east/.../000020061606A0614750.php.>[2 February 2009]

- Alabdalla, M. (2005)' Chemical Characterization of Counterfeit Captagon Tablets seized in Jordan.' *Forensic science International* [online] 152, 185-188. Available from<http://www.sciencedirect.com> [28 Feb 2009]

- Alfadl, A.A. Abdoon S, Elamin M, and Gar Elnabi N. (2006)'Quality of Anti-malarials Drugs in Sudan: Results of Post-Marketing Surveillance.' *Sudanese Journal of Public Health1*, (2).

- Al-Hussaini, SR. (1996)' Counterfeit Captagon: an Analytical Study.' *Science& Justice* 36, (3) 139-142. [Online] Available from < http://www.scienceandjusticejournal.com/article/S1355-0306 (96)72588-1.> [30-January 2010]

- Al-Iryani A. and Ba-swaid, H. (2009)' some 30-40% of Medicines Sold locally is counterfeit' *Saudi Gazette* [online] available from <http://www.saudigazette.com.sa/index.cfm?method=home.> [9-May -2009]

- Amin, A.A. and Kokwaro, G.O. (2007) 'Anti-malarials Drug Quality in Africa.' *Journal of Clinical Pharmacy and Therapeutics* 32, (5) 429-440. [Online] Available from <http://www.ingentaconnect.com/content/bsc/jcpt/2007/00000032/00000005/art00002?> Crawler=true [9-May 2009]

- Andrew, J. (2007) 'Bitter Pills.' *Pub Med Central Journal* [online] 335, (7630) 1120-1121 Available from <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2099530> [9-may2009]

- Appleby J. and Sternberg S. (2002) "Statin side effect rare, but be aware "*USA TODAY* Available from <http://www.usatoday.com/money/markets/2002-08-18-statin-effect_x.htm>[2009-10-06]

- Arfwedson J. (2004) '*Parallel Trade in Pharmaceuticals*' A Policy Report 182. Texas-United States: Institute for Policy Innovation

- Bader R. (2004) *Medicine Prices, Availability and Affordability in Jordan*. Report of a survey conducted in 2004 in Amman, Irbid, Zarqa and Karak using the WHO/HAI Price measurement methodology [online] <http://www.emro.who.int/dsaf/dsa786.pdf > [1June 2010]
- Bate, R, Coticelli PH, Tren R and Attaran A. (2008)'Anti-malarials Drug Quality in the Most Severely Malarious Parts of Africa- a Six Country Study.' *PLoS One* [Online] 3 (5) Available from<http://www.plosone.org/article/info:doi%2F10.1371%2Fjournal.pone.0002132> [10 April 2009]
- Beermann B, Groschinsky-Grind M, Rosén A. (1976). "Absorption, metabolism, and excretion of hydrochlorothiazide". *Clin Pharmacol Ther* 19 (5 (Pt 1)): 531–7.
- Berger PB. (2007) 'The Theinopyridines in Coronary Artery *Diseases' Current Cardiology Reports* 1, (3) 192-198.
- Bogdanich W. (2007)' Free Trade Zones Ease Passage of Counterfeit Drugs to U.S.' *The New York Times* 17 December.
- Briggs GG, Nageotte MP (2001). "Fatal fetal outcome with the combined use of valsartan and atenolol". *The Annals of Pharmacotherapy*35 (7-8): 859–61. doi:10.1345/aph.1A013. PMID 11485133.

- Catizone C. A. (2006) 'Counterfeit Drugs and States' Effort to Combat the Problem.' *Journal of Pharmacy Practice* 19, (3) 165-170.

- Caudron J.M., Ford N., Henkens M., Mac C., Kiddle-Monroe R., and Pinel J. (2008) 'substandard medicines in resource-poor settings: a problem that can no longer be ignored.' *Tropical Medicine and International Health* 13, (8) 1062-1072.

- Clarck, E. (2008)'Counterfeit Medicines: The pills that Kill.' *Telegraph co.uk* 5 April

- Celia, F. (2005) 'States Move to Comply with Drug Pedigree Laws' *Drug Topics* 6 June

- Cockburn R., Newton PN. ,Agyarko EK., Akunyili D., and White NJ. (2005) 'The Global Threat of Counterfeit Drugs: Why Industry and Governments Must Communicate The Dangers.' *PLoS Medicine Journal* [online] 2(4) Available from <http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1062889&blobtype=pdf>[10 may 2009]

- Cockburn R. (2005) 'Death by Dilution' *the American Prospect* [Online] available from<http://www.prospect.org/cs/articles?articleId=10650> [29 April 2009]

- Crooker K. (2009) 'RFID Technology as Sustaining or Disruptive Innovation: Applications in the Healthcare Industry.' *European Journal of Scientific Research* 37, (01)160-178.

- Dahiya, S. (2008)'Counterfeit Medicines- The Global Hazard.' *Pharmainfo.net*[online] 6, (4) available from<http://wwwpharmainfo.net/reviews/counterfeit-medicines-global-hazard>[5 Dec.2009]

- Deisingh AK. (2005) 'Pharmaceutical Counterfeiting' *the Analyst* 130, 271-279.

- Deus L. (2006) 'Technological Roles in Combating Drug Diversion and Counterfeiting' *Journal of Pharmacy Practice* 19, 146.

- Falrbalrn D, Shum A, Schonlg W, and Milbradt C (2007)' Intellectual property and the fight against Counterfeit drugs' from Innovation to Commercialization 2007.*A supplement to Intellectual Asset Management Magazine*,www.iam-magazin.com.

- Gaudiano, MC. Maggio AD, Cocchieri E, Bertocchi P, Alimonti S and Valvo L (2007).'Medicines informal market in Congo, Burundi and Angola: Counterfeit and substandard anti-malarials.' *Malaria Journal* [online] 6(22) available from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810297> [28 January 2010]

- German Pharma Health Fund (GPHF) (2004)' *Counterfeit Medicines- An unscrupulous Business*' [on line] Germany: Merck, Darmstadt. available from <http://www.gphf.org/web/en/minilab/hintergrund_arzneimittelfaelschungen.htm> [August 7 2009]

- Ghosn, Z. (2008) 'Lebanon Launches Campaign to Counter Fake Drugs.' Science and Development Network [online] available from <http://www.scidev.net/en/health/standards-of-care/lebanon-launches-campaign-to-Counterfakedrugs.html?utm_source=link&utm_medium=rss&utm_campaign=en_health _standardsofcare launches campaign to counter fake drugs. > [July 13 2009]

- Global Intellectual Property News Agency *Ag-Ip news* (2009)'JFDA Seizes Counterfeit Medicines, Shuts Down 180 Pharmacies in Jordan' 3 February

- Green, M., Mount, D. and Wirtz, R. (2001) 'Authentication of artemether, artesunate and dihydroartemisinin anti-malarials tablets using simple calorimetric method*' Tropical Medicine and International Health*6, (12) 980-982.

- Hall, R. (2009) 'Drug Companies Attack Fake Medicine' Daily Star 17 December.

- Halteh S. (2008)'Unified Efforts Needed to Combat Counterfeit Medicines in Jordan.' *Ag-Ip News*[Online] available from <www.ag-inews.com/GetArticle.asp?Art_ID=5736&lang=en> [15 April 2009]

- Ho CH. And Lin G. (1996)'Stability-Indicating High Performance Liquid Chromatographic Assay Method for Drugs in Pharmaceutical Dosage Forms: Part 1' *Journal of Food and Drug Analysis* 4(4):271-292.

- Humphreys A. (2010) ‘200: *World’s Best Selling Medicines-Sales’* Med Ad News Guide to Pharmaceutical Marketing and Interactive Services.

- IFPMA (International Federation of Pharmaceutical Manufacturers & Associations (2006)' Conference on’ Corporation in Combating Health Threat Posed by Counterfeit Medicines.' *Rome* News *Release* (2006) Guy W. (ed.) Geneva, Switzerland.

- IMS (International Market Statistics (2010) A Report on Sales Screening in Jordan. Amman : Jordan

- Ivanovic D., Malenovic A., and Jancic B. (2007) ‘Monitoring of Impurity Level of Valsartan and Hydrochlothiazide Employing an RP-HPLC Gradient Mode.’ *Journal of Liquid Chromatography & Related Technologies* 30, 2879-2890.

- JFDA Jordan Food and Drug Administration (2008). The Hashemite kingdom of Jordan. *Public Health Law* No 47.

- Jordan NHRHO (2009) National Human Resources for Health Observatory available from:[on line]<http//www.jordannap.net/hhc/nhrho/index.asp?it=2&m=2>[5-Dec.2009]

- Kelesidis Th., KelesidisI., Rafailidis PI., and Falagas ME. (2007) ‘counterfeit or substandard antimicrobial Drugs: a review of the scientific evidence.’ *Journal of Antimicrobial Chemotherapy* [online]

available from <http://Jac.oxfordjournals.org/cgi/reprint/dkm109vl> [23july 2009]

- Khan, A. and Ghilzai, K. (2007)' Counterfeit and Substandard Quality of Drug: The need for an effective and stringent regulatory control in India and other developing countries.' *Indian Journal of Pharmacology*39, (4) 206-207.

- Kontnik LT. (2006 a)'Manufacturer and Industry Responses to Counterfeiting' *Journal of Pharmacy Practice*19, (3) 141.

- Kontnik LT. (2006 b)'Manufacturer and Industry Responses to Counterfeiting' *Journal of Pharmacy Practice*19, (3) 145.

- Kyriacos, S. Mroueh M, Chahine P. and Khouzam O. (2008).'Quality of amoxicillin formulations in some Arab countries.' *Journal of Clinical Pharmacy and Therapeutics*33,(4) 375-379 [Online] available from <http://www3.interscience.wiley.com/journal/120749538/abstract > [5 May2009]

- Lancaster I. (2008)'Holograms and Anti- counterfeiting Sophisticated replication techniques have made counterfeiting and fraud a serious threat to the pharmaceutical industry' *Pharma Tech.*

- Lon, C.T., Tsuyuoka R, Phanouvong S, Nivanna N, Socheat D, Christophel E.M. and Smine A. (2006). 'Counterfeit and Substandard anti-malarials Drugs in Cambodia.' *Transaction of the Royal Society of Tropical Medicine and Hygiene* 100, (11) 1019-1024.

- Lybecker, K. (2007)' RX Roulette: Combating Counterfeit Pharmaceuticals in Developing Nations.' *Managerial and Decision Economics Journal* [Online] 28, (4-5)509-520. Available from< http://www.interscience.wiley.com>[12 May 2009]

-Marks JW (2007).''Valsartan'' *MedicineNet.Com* available [online from<http://www.medicinenet.com/valsartan/article.htm.[2010-03-04]

- Martijn T.H. (2003)'Health Risks of Counterfeit Pharmaceuticals.' *Drug Safety* [online] 26, (14) 991-997 available from< http://adisonline.com/drugsafety/Abstract/2003/26140/Health_Risks_of_Counterfeit_Pharmaceuticals.1.aspx> [December 10-2009]

- Mason, P. and Ali, A. (2005) 'Pharmaceutical Chaos' *The Pharmaceutical Journal* [online] 274 (7334) 115-116 available from< http://www.pharmj.com/pdf/articles/pj_20050129_iraq.pdf>[May 15, 2009]

- Medicine Net.Com (2010) *Medications and Drugs* [online] available from<http://www.medicinenet.com/statins/article.htm> [22 May 2010]

- (MHRA) 2006 'Guidance for Pharmacists: how to detect and report Counterfeit Medicines.' *Pharmaceutical Journal* [online] 276, 627-628.Avialable from <http://www.pharma.com/pdf/articles/pj_20060527_guidance.pdf> [June 6 2009]

- Mohan A, Hariharan M, Vikraman E, SubbaiahG,Venkataraman BR, and Saravanan D.(2008) 'Identification and Characterization of a principal Oxidation impurity in clopidogrel drug substance and drug product.' *Journal of Pharmaceutical & Biomedical Analysis* 47(1), 183-189.

- Morei R. (2009) 'Counterfeit Medicines' *addounia* [online] available from: <www.addounia.tv/article.jsp?smcache=true&id=247> [Dec.12-2009]

- Mornar A., Damic M. and Nigovic B. (2010) 'Separation, Characterization and Quantification of Atorvastatin and Related Impurities by Liquid Chromatography-Electro spray Ionization Mass Spectrometry.' *Analytical Letters* 43, (18) 2859-2871.

- Morris, J. and Stevens, Ph. (2006)' Counterfeit medicines in Less Developed Countries: Problems and Solutions.' International Policy Network London, UK.

- Newton P. Green MD, Fernandez F, Day NPJ, and White NJ. (2006a) 'Counterfeit anti-infective Drugs.' *Lancet Infectious Diseases* [Online] 6, (9)602-613.Available from<http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(06)70581-3/fulltext> [25 February 2009]

- Newton, PN, McGready R, Fernandez F, Green MD, Sunjio M, et al. (2006 b) 'Manslaughter by Fake Artesunate in Asia- Will Africa Be Next?'.*PLoS Medicine Journal* [online] 3, (6) Available from: <http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.0030324;jsessionid=EDA02AC766EB0473ACBBDB4700F3EEC4> [25 February 2009]

- Newton, P. Fernandez FM., Plancon A., Mildenhall DC., Green MD., Ziyong L., Christophel EM., Phanouvong S., Howells S., McIntosh E., Laurin P., Blum N., Hampton Ch., Faure K., Nyadong L., Soong C.W., Santoso B., Zhiguang W., Newton J. and Palmer K.,(2008) ' A collaborative Epidemiological Investigation Into the Criminal Fake Aretesunate Trade in South East Asia.' *PLoS Medicine Journal* [online] 5, (2) Available from <http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.0050032>[24 February 2009]

- Obaid, A. (2009).'Quality of Ceftriaxone in Pakistan: Reality and Resonance.' *Pakistan Journal of Pharmaceutical Sciences* 22, (2) 220-229.

- Onwujekwe O. Kaur H, Dike N, Shu E, Uzochukwu B, Hanson K, Okoye V and Okonkwo P. (2009).'Quality of Anti-malarials drugs provided by Public and Private health care providers in South-East Nigeria.' *Malaria Journal* [on line] 8, (22) available from <http://www.malariajournal.com/content/8/1/22>[26 march 2009]

- Pereillo J, Maftouh M, Andrieu A, Uzabiaga M, Fedeli O, Savi P, Pascal M, Herber J. Maffrand J and Picard C.(2002) "Structure and Stereochemistry of the active Metabolite of Clopidogrel" *Drug Metabolism and Disposition*[online] 30, (11): 1288–1295 Available from http://dmd.aspetjournals.org/content/30/11/1288.full.pdf [22 September 2011]

- Public Health and Pharmacy Law (2008), Amman: Law No.47 Section 7.

- Royal Decree (2001) the Hashemite Kingdom of Jordan. *Drug & Pharmacy Law*. Amman: Provisional law No.80

- Rudolf, PM. Bernstein, IB. (2004) 'Counterfeit Drugs.' *The New England Journal of Medicine*. [Online] 350, (14)1384-1386.Avialable from <http://content.nejm.org/cgi/reprint/350/14/1384.pdf?ijkey=bad27726da332c6a35be35cabd1a58b9b5018c54> [9 may2009]

- Sabag R. (2008) 'Lack of legislations, lack of coordination is the factors behind the selling of counterfeit pharmaceuticals.' *Al-Arab alyoum*8 February: 8

- Simon T; Verstuyft, C; Mary-Krause, M; Quteineh, L; Drouet, E; Méneveau, N; Steg, PG; Ferrières, J et al. (January 2009). "Genetic Determinants of Response to Clopidogrel and Cardiovascular Events". *The New England Journal of Medicine***360** (4): 363–75. doi:10.1056/NEJMoa0808227. PMID 19106083.

-Stevens Ph. (2006) 'Counterfeit Drugs: getting to the root of the Problem' *Medical Progress Today* 24 March.

- Tipke, M., Diallo, S., Coulibaly, B., Storzinge, D., Hoppe-Ticky, T., Sie, A., and Muller, O. (2008)' Substandard Anti-malarial Drugs in Burkina Faso.*' Malaria Journal* [on line] 7, (95) available from <http://www.malariajournal.com/content/7/1/95> [25-march2009]

- U.S. Pharmacopoeia (2004) A *Review of Drug Quality in Asia with Focus on Anti-Infectives.* 'BS' the Standard for Quality. United States

- U.S. Pharmacopoeia (2006) Material Safety Data convention.

- U.S. Pharmacopoeia (2010) *what is Pharmacopoeial Forum?* United States

- USP Monographs (2007)Pharmacopoeia Forum volume 29(3) pp.609 [online] available from<http://www.pharmacopeia.cn/v29240/usp29nf24s0_m9792.html>

- US Pharmacopoeia (2011) USP's Pending Monographs Guideline. Available from< http://www.usp.org/pdf/EN/pendingStandards/m5601.pdf>

- Walt, B. (2007) 'Free Trade Zones Ease Passage of Counterfeit Drugs to U.S.' *The New York Times* 17 December

- Wertheimer, A. and Norris, J. (2009)' Safeguarding against Substandard/ Counterfeit drugs: Mitigating a macroeconomic pandemic.' *Science Direct research in Social and Administrative Pharmacy* [Online] 5, (1) 4-16. Available from <http://www.sciencedirect.com/science?_ob=ArticleListURL&_method=list&_ArticleListID=930585366&_sort=d&view=c&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=24d3f1e0e6c426e30cf6e8eafc59a140>[10 June2009]

- Williams RL. (2006) 'US Pharmacopoeia Council of Experts 2005-2010: Work Plans, New Revision Approaches, and Other Enhancements.' *AAPS Journal.* 2006; 8(4): 661-664.

- World Health Organisation (1999*)* A Report on Counterfeit Drugs*: Guidelines for the development of measures to combat counterfeit drugs WHO/EDM/QSM/99.1*.Geneva: Switzerland.

----- (2003a), Counterfeit *Drugs* Fact Sheet, Nov.2003. Geneva: Switzerland.

----- (2003b) *The Quality of Anti-malarials- A Study in Selected African Countries' Essential Drug and Medicines Policy* Series N 030. Geneva: Switzerland.

----- (2005) Counterfeit Medicines Geneva: Switzerland.

----- (2006 a) *Counterfeit Medicines* Fact Sheet N 275. Geneva: Switzerland.

----- (2006 b) *Quality assurance of pharmaceuticals; a compendium of guideline and Related materials*. Vol 2, Geneva: Switzerland.

----- (2007 a) *General Information on Counterfeit Medicines* Geneva: Switzerland.

----- (2007 b) *'Essential Medicines List (EML)'* Fact sheet N 325. Geneva: Switzerland

----- (2008) 'Drug *Information*' vol22, No.2. Geneva: Switzerland.

----- (2009) Regional office for the Eastern Mediterranean, *Country Profiles* Geneva: Switzerland.

------ (2010)' Epilepsy in the WHO Eastern Mediterranean Region' Regional Office for the Eastern Mediterranean, Cairo.

- Young, D. (2004).'Counterfeit drugs lawsuit point's finger at wholesaler, pharmacy.' *American Society of Health System Pharmacists* [Online] 61, 1980-1987. Available from <http://www.ashp.org/import/news/HealthSystemPharmacyNews/newsarticle.aspx?id=1667> [10 February 2010]

- Zyiadat, A. (2009) 'closing down 33 pharmacies for the last five months of this year.' *Al arab Al youm*20 June-2009.

APPENDICES

APPENDIX A

BACKGROUND ABOUT JORDAN

Background about Jordan

Jordan is situated in the Middle East, bordered to the north and north-east by Syria and Iraq, to the south by Saudi Arabia and Gulf of Aqaba, and to the west by the occupied west bank.

Jordan Map

The total population was 5.85 million in 2008, with a 2.3% annual growth rate.

The majority of the population (83 %) lives in urban areas, and life expectancy at birth was 73 years in 2008, with 3.2% of the population over the age of 65 years (WHO 2009).

Jordan is classified as a lower-middle income country with a GDP per capita of US$ 2672 (WHO 2009).The total expenditure on health services in 2008 accounted for 9.6% of the GDP (WHO 2009).

In 2003, the expenditure on pharmaceuticals in Jordan was JD 211 million (about US$ 295 million. Over the last 5 years, the average growth rate has been about 3%. This is due to increasing medicine costs and consumption rates (Bader 2004).

The health system in Jordan consists of public, private and nonprofit organisations.

But the main provider of health services is the public sector which consists of:

- Ministry of Health (MOH), the main provider of health care, which provides coverage for public employees and their dependants, other individuals, certified as poor, and disabled.
- The Royal Medical Services (RMS), which provide coverage for military personnel and their dependants, and other referrals from MOH.
- Other smaller public programs include several universities-based programs, such as Jordan University Hospital (JUH) in Amman and King Abdullah Hospital (KAH) in Irbid, which provide coverage for university employees and their dependants.

The public health sector is composed of tertiary hospitals, primary health care centers, and rural health posts (Bader 2004).

The private sector provides coverage for companies, employees either through self-insuring or through the purchase of private health insurance.

Local nonprofit Organisations: charitable organisations such as the non-government organisations (NGOs), Zakat Fund (Islamic alms giving), and other charitable societies.

International agencies: which offer free medical services include United Nations Relief and Works Agency (UNRWA), charitable societies under the umbrella of the General Union of Voluntary Societies (GUVS), and the foreign community centers administered with assistance from international groups such as Caritas and Radda Barnen (Swedish Save the Children) (Jordan NHRHO 2009).

Usually 68% of Jordan's population is formally covered through various health insurance programs: public sector 48% private sector and UNRWA 20% programs, while 32% has no formal coverage. Yet, these individuals can purchase services at MOH facilities at highly subsidised prices (WHO 2009).

The Jordanian pharmaceutical market consists of imported pharmaceuticals, which represents 75% and local manufactured pharmaceuticals, which represent 25%. Most of the locally manufactured pharmaceuticals are generic, which are usually sold under commercial name (branded generics).

About 5% of the local pharmaceutical products are manufactured under license through an agreement with the originator brand manufacturer and there is some local labeling and packaging undertaken using products supplied in bulk from the originator company.

Public sector pharmacies are attached to health centers or public hospitals. The private sector is composed of independent community pharmacies and chain pharmacies as well as hospital pharmacies located in private health facilities.

The sale of medicines is regulated by Pharmacy and drug Law as enforced by Jordan Food and Drug Administration (JFDA). Prices of medicines are regulated and registration of a product does include setting of prices which is normally lower for locally manufactured medicines (Bader 2004).

APPENDIX B

DEFINITIONS OF COUNTERFEIT DRUS IN MANY COUNTRIES

Definition of counterfeit drugs in many Countries

In Nigeria for example, counterfeit was defined (WHO 2007a) as:

Any drug product which is not what it purports to be; or any drug or drug product which is so colored, coated, powdered or polished that the damage is concealed or which is made to appear to be better or of greater therapeutic value than it really is, which is not labeled in the prescribed manner or which label or container or anything accompanying the drug bears any statement, design, or device which makes a false claim for the drug or which is false or misleading; or any drug or drug product whose container is so made, formed or filled as to be misleading; or any drug product whose label does not bear adequate directions for use and such adequate warning against use in those pathological conditions or by children where its use may be dangerous to health or against unsafe dosage or methods or duration of use; or any drug product which is not registered by the Agency in accordance with the provisions of the Food, Drugs and Related Products" (Registration, etc.) Decree 1993, as amended.

In Pakistan counterfeit drug was defined as:

"..a drug, the label or outer packing of which is an imitation of, resembles or so resembles as to be calculated to deceive, the label or outer packing of a drug manufacturer."

In the Philippines, the Republic Act No. 82036 defined counterfeit drug/medicine to mean:

..."Medical products with correct ingredients but not in the amounts as provided there under, wrong ingredients, without active ingredients, with insufficient quantity of active ingredients, which results in the reduction of the drug's safety, efficacy, quality, strength or purity.

It is a drug which is deliberately and fraudulently mislabeled with respect to identity and/or source or with fake packaging, and can apply to both branded and generic products.

It shall also refer to the drug itself, or the container or labeling thereof or any part of such drug, container or labeling bearing without authorisation the trademark, trade name or other identification mark or imprint or any likeness to that which is owned or registered in the Bureau of Patent, Trademark, and Technology Transfer in the name of another natural or juridical person a drug product refilled in containers by unauthorised persons if the legitimate labels or marks are used. An unregistered imported drug product, except drugs brought in the country for personal use as confirmed and justified by accompanying medical records, and a drug which contains no amount of or a different active ingredient, or less than 80% of the active ingredient it purports to possess, as distinguished from an adulterated drug including reduction or loss of efficacy due to expiration."

The United States Federal Food, Drug and Cosmetic Act' defines a counterfeit drug as,

"...a drug which, or the containers or labeling of which, without authorisation, bears the trademark, trade name, or other identifying mark, imprint, or device or any likeness thereof, of a drug manufacturer, processor, packer, or distributor other than the person or persons who in fact manufactured, processed, packed, or distributed such drug and which thereby falsely purports or is represented to be the product of, or to have been packed or distributed by, such other drug manufacturer, processor, packer, or distributor" (WHO 2007).

APPENDIX C

THE NEW REGULATIONS VERSUS THE OLD REGULATIONS

New regulation versus the old regulation

The "Pharmacy practice law" was established in 1972 and implemented since then. The pharmacy profession faced many challenges; the most important one was the trade and manufacturing of counterfeit pharmaceuticals. The law did not have any specific description for counterfeit pharmaceuticals due to the fact that, these products were not known at that time therefore no punishments were mentioned. When any unlawful counterfeit like act was encountered, judges were empowered by law to deal with it on a case by case basis as a smuggling issue.

In the year 2001 a provisional law called "drug and pharmacy law" was enacted. The law has the following relevant articles:

Article 90

"In case of any violation by the Pharmacist in charge of the provisions of this law, the Minister or his deputy may, under the inspector's report, take the following actions:-

- Giving notice to such pharmacist.
- Warning such pharmacist.
- Refer the pharmacist to the Disciplinary Council of the Jordan Pharmacist Association.
- Refer the pharmacist to the Competent Court. (Provisional law 2001)"

Article 92

"Any pharmacist who commits the following violations has to be referred to the Association's Disciplinary Council and shall be punished by the following penalties:-

Payment of a fine in the sum of (250 – 500) Dinars in case he, in contravention of the provisions of this law, would:

- In case of publishing and advertising without the consent of both the minster and the Association.
- Display in his pharmacy any expired drugs where the Ministry shall have the right to seize those drugs when discovered.
- Fail to observe the prices determined for any drugs, and any other items priced by the Ministry.

Sell or venture to sell any medical free sample."

Article 92

"The Ministry, by a justifying recommendation from the director, may close any public or private pharmacy or drugstore wherein a violation had been committed, or he may suspend the breaching pharmacist from practicing this profession until such violation has been removed or an absolute judgment has been issued by the court to that respect." (Provisional law 2001)

In 17th of August 2008, a new regulation for public health was established and implemented. These new regulations have provided a legal definition for counterfeit pharmaceuticals for the first time in the history of the country (JFDA 2008).

The new regulations have emphasised many dimensions that assumed to be effective when regulatory authorities enforce them into implementation. These dimensions are as follows:

Article number 31 stated that, the medicine is considered to be counterfeit when:

The medicine is produced in an unauthorised place or produced in a different company or without the permission of the originator company.

The medicine does not contain an active ingredient or a different level from the active ingredient, or another ingredient instead of the active ingredient indicated on the label.

The medicine has a counterfeit trademark or a counterfeit pedigree papers.

The production area is different from the real production area on the label.

Article number 32 stated that, it is prohibited and considered to be against the law to deal with or to import or to enter any counterfeit medicine to the Kingdom and that includes: The free trade zones, the "transit" areas, and borders. It is also prohibited to advertize or to publicize any counterfeit medicine.

Article number 33 stated that:

1- Despite previous legislation, The General Director for Food and Drug Administration issues an order that prohibits dealing with any smuggled or counterfeit medicine.
2- The General Director of Food and Drug Administration (FDA) can delegate any specialised employee within the administration or the ministry of health to inspect and draw samples from local or imported medicine against a receipt within the rules in order

to analyse and test this medicine to assure that it complies with the manufacturer standards.

Article number 34 stated that:

1- If the medicine is found expired or unsuitable for human use after examination of the medicine, the Food and Drug Administration must seize the medicine when discovered in possession of the pharmacy.
2- The Court makes a decision to seize the counterfeit or smuggled medicine.
3- The general director will assign one of the inspector pharmacists to supervise the disposal of the counterfeit or the smuggled drug. The new law has also specified certain punishments which includes imprisonment or paying fine up to the judge to decide on the type of punishment

Article number 65 stated that:

If the person convicted by buying or selling or exporting counterfeit medicine to the kingdom, he will spend a period not less than 3 years and not more than 5 years in prison with hard work, or the convicted individual will pay a fine not less than JD 1000, and not more JD 5000, or both penalties. In some serious circumstance, the fine will be twice as much as the price of the confiscated counterfeit drug.

The person who convicted of publicizing any counterfeit drug will be jailed for not less than one month and not more than 6 months or will pay fine not less than JD 1000 and not more than JD 3000 or both penalties.