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Counterfeiting: A Challenge to Forensic Science, the Criminal Justice System, and Its Impact on Pharmaceutical Innovation

Pauline Elizabeth Leary
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**COUNTERFEITING: A CHALLENGE TO FORENSIC SCIENCE,
THE CRIMINAL JUSTICE SYSTEM, AND ITS IMPACT ON
PHARMACEUTICAL INNOVATION**

by

PAULINE ELIZABETH LEARY

A dissertation submitted to the Graduate Faculty in Criminal Justice in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

2014

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This manuscript has been read and accepted by the
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ABSTRACT

COUNTERFEITING: A CHALLENGE TO FORENSIC SCIENCE, THE CRIMINAL JUSTICE SYSTEM, AND ITS IMPACT ON PHARMACEUTICAL INNOVATION

by

PAULINE ELIZABETH LEARY

Adviser: John A. Reffner, Ph.D.

Counterfeit drugs threaten public health and present unique and complex challenges to the criminal justice system and the field of forensic science. Theft of intellectual property in the pharmaceutical industry has caused sickness and death, and it is necessary that the perpetrators of these crimes are brought to justice. In some cases, threats to health and safety are short term; in others they are long term. This research describes these threats in detail.

The problem is complex, and there are many important factors that need to be considered to successfully address the problem. Public-health challenges, drug-development challenges, legal challenges, issues of public policy, and financial considerations are all important aspects of the problem that need to be understood. This research describes these details so that appropriate solutions can be proposed.

The field of forensic science struggles to establish analytical methods to identify composition and establish provenance of counterfeit goods. No method has been shown to be universally applied to achieve this goal. The use of field-portable instruments to detect and

identify counterfeits in the field is important emerging technology. These instruments must work quickly and accurately. This research defines the challenges faced by the field of forensic science and proposes methods that may be used to address these challenges. This will enable forensic scientists to provide support to law enforcement and other members of the criminal justice and legal systems to successfully investigate and adjudicate these crimes.

This dissertation is dedicated to
Mary and Jack Fogarty

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CHAPTER 1: INTRODUCTION

Counterfeit and substandard drugs present unique and complex challenges to the fields of forensic science and criminal justice. These goods seriously threaten public health and safety. Analytical testing can be challenging because forensic analysis of counterfeit drugs typically goes beyond more traditional pharmaceutical methods of drug analysis. Criminal justice and law-enforcement organizations are being forced to evaluate current policies and practices so successful investigation and adjudication in these types of cases is possible. The internet has made it possible to easily access these drugs even in places like the United States that have a well-controlled legitimate pharmaceutical supply chain. The problem is multidimensional and incorporates matters of law, science, criminal justice, public health, and public policy. There is a need to delineate the integral aspects of the counterfeit drug trade if an effective solution is to be proposed.

Detection and identification of counterfeit drugs is a critical step in the process of addressing the counterfeit-drug problem. The ability to individualize is the foundation of the discipline of criminalistics and typically the goal of the forensic scientist. Classification is also important. (De Forest, Gaensslen, & Lee, 1983) Scientific testing performed to achieve these goals must use methods that work accurately and reliably. Analytical testing of counterfeit drugs in the field is usually performed to differentiate an authentic from a non-authentic article and to classify these goods. This capability has value and may help determine source or origin. In situations where evidence will be used court, technologies and methods used must meet the standards of admissibility of scientific evidence. Historically, results of tests performed using field instruments were used in a presumptive manner (Fedchak, 2014) to support investigations and for probable cause. More recently, the need to collect court-admissible data in the field is

desirable because it may save time and money in the long term. Another significant advantage of the use of diagnostic field tests is the ability to deal with “dissipating evidence” such as gunshot residue or explosive traces on the hands of suspects. (Almog, 2006) When analyzing counterfeit drugs, additional considerations make the forensic testing of these goods in the field important. This testing is unique and challenging.

When analyzing a drug in a pharmaceutical setting to confirm identity, infrared or mass spectra may be collected from the sample and used for identification. An additional routine test may then be used to quantify the amount of drug present or establish its distribution throughout the final dosage form. Once the tablet is identified and quantified using standard test methods that were developed during the drug-development process, analysis is usually complete. When analyzing counterfeit drugs in a forensic setting, however, identification of the active pharmaceutical ingredient (API) is likely only one of many steps in the analytical work flow. Analysis of counterfeits may begin with the evaluation of packaging used. A comparison of coatings on laminates used for both dosage form and bulk packaging may serve as a means for differentiation. Physical comparisons of markings and other sample features may also be used for this purpose. Once inside the packaging, physical and chemical characteristics of the dosage form may then be evaluated. If the API is present, further testing is likely required. Counterfeits may have the proper API in the wrong dosage or solid-state form. Solid-state form of the API is important for a variety of reasons. An example is polymorphism where different polymorphs of the same chemical may exhibit different bioavailability. The polymorphic form created during manufacture may also have legal significance because one polymorphic form may be covered under patent whereas others may not. In the case of different solid-state hydrates of the API, the wrong hydration level may result in under dosing tablets when hydration levels are too high, or

over dosing tablets when hydration levels are too low. In addition dosages and solid-state form differences, particle size or distribution throughout the dosage form may be different, or residual solvents present may be different. These differences may be used as points of comparison amongst samples. When evaluating counterfeits, the inactive ingredients may be different from the authentic versions of the drug and need to be identified and characterized. Foreign particles present in the counterfeit versions may serve as an additional feature for differentiation and identification. In these cases, non-routine methods of analysis need to be employed.

The analytical testing of counterfeit drugs is also unique because it is typically the goal of the forensic scientist to establish provenance when counterfeit drugs are presented for analysis. No method or combination of methods has been shown to be universally applied to achieve this goal. Attempts are usually made to link samples to each other using some chemical or physical marker present in the sample. (Alabdalla, 2005; Lopatka & Vallat, 2011; Ortiz, et al., 2011) These attempts have been extended to the sourcing of illicit drugs as well. Creating these links between samples is important. Counterfeiters are frequently members of terrorist organizations or organized crime groups. (United Nations Office on Drugs and Crime, 2014) Establishing distribution chains and linking samples from different geographic locations may help bring justice. This justice may be important criminally, for example, in cases when counterfeits cause harm or death; or they may be important in civil cases where patent-infringement violations have cost brand owners significant costs for which they seek compensation. A significant limitation of all methods currently used to establish provenance is in the limited number of samples available for analysis for any given study. (Pérez-Bernal, Amigo, Fernández-Torres, Bello, & Callejón-Mochón, 2011) Testing of samples in the field and creation of a mechanism for law-enforcement agencies from different locations to share this data would be very valuable, and

would provide the forensic scientist with access to larger numbers of samples. These shared data could be used for comparisons, to evaluate trends, and perform other types of data review useful in establishing provenance.

The counterfeit-drug problem is also complex because of both the patenting system and laws governing patented drugs. In the United States, patents are granted through the United States Patent and Trademark Office (USPTO) and are integrated within the development lifecycle of pharmaceutical innovators and generic manufacturers. The United States patenting system as applied to the pharmaceutical industry was completely redefined by The Drug Price Competition and Restoration Act of 1984, also known as the Hatch-Waxman Act. This law was designed to protect rights of innovators, while at the same time allowing for generic drugs to come to the market as quickly as possible. It fundamentally changed the patenting system in the United States and has had a significant impact on patenting of pharmaceutically relevant compounds, drug development, the Food and Drug Administration (FDA) regulatory process, pharmaceutical litigation, patent protection, and patent enforcement. It is important that the patenting and drug development processes, and specifically the impact of the Hatch-Waxman Act on these processes, is understood. The impact of counterfeit drugs on criminal justice and forensic science are directly related to both patenting and drug development.

While it is important to understand the patenting process and its integration with drug development, understanding the value of patents is also important. Patents are granted because the patented invention will provide a benefit to society. This is especially true in the pharmaceutical industry. Drugs patented in the United States are developed and tested in accordance with FDA guidelines with the intention of bringing the patented invention to the market in the form of a new drug. Without these patented inventions, society loses and the

future of pharmaceutical development is challenged. Pharmaceutical innovation is an important part of society. It helps cure and treat disease, and improves quality of life. New drugs will be needed to remedy the health problems being created and perpetuated by the presence and proliferation of counterfeit and substandard drugs in many regions of the world. In places like Africa and Asia, anti-infective medicines containing sub-therapeutic amounts of API are commonly encountered. These bogus drugs, whether counterfeit or substandard, increase the risk of the spread of resistance of disease to available drugs. (Newton, et al., 2006) Sub-therapeutic amounts of drug promote resistance. This factor, coupled with other issues that indicate diseases like malaria are impacted by environmental change (Siraj, et al., 2014), makes the counterfeit-drug problem even more troubling.

The future of pharmaceutical innovation is in question. The drug-development life cycle is long, risky, and expensive. It seems fair to question the future of pharmaceutical innovation and the development of new medicines in a global environment where intellectual property (IP) rights are not protected and enforced. These rights are an inherent aspect of the counterfeit-drug problem. Therefore, it is important that the role patents and protection of patent rights play both nationally and internationally are understood.

Counterfeit drugs present challenges to practitioners of law and justice. Identification and prosecution of criminals responsible for the infiltration of counterfeit drugs into the market is extremely challenging for a variety of reasons. For instance, determination of source or origin of the drug is not easy, especially considering the global nature of this problem. In situations where determination of source is possible, local laws and jurisdictional issues frequently hamper prosecution. In addition, prosecution of counterfeiters is almost impossible in some regions of the world where IP rights are meaningless. Even in places like the United States, enforcement of

IP protection for non-pharmaceutical products can be very difficult and require a level of diligence on the part of the brand owner not usually required of victims of crimes. While some relate these cases to being civil cases, IP rights are protected by law and breaking them is a criminal activity. (Carruthers & Ariovich, 2004) For pharmaceutical products, FDA regulations highlight the criminal aspect of this problem a little bit better. While brand owners may have an unusual burden to achieve criminal justice, there is, at least, a regulatory, judicial, and legal framework in the United States within which these issues may be addressed. Pharmaceutical suppliers governed by FDA must adhere to and work in the United States legal and regulatory systems. Within this jurisdiction, regulations require that suppliers adhere to certain guidelines and meet minimum safety, efficacy, and other criteria in order to receive approval to sell pharmaceutical drug products to the American consumer. If these guidelines are not met, laws and statutes are in place to ensure that these drug products are not legally available for sale.

Interestingly, although historically the United States has experienced a tightly controlled pharmaceutical supply chain, the FDA appears to be exercising more stringent control over manufacturing sites located overseas. (Harris, 2014; Siddiqui & Chatterjee, 2014) Although firms that legally supply drugs to the United States have always been governed by FDA, inspections of these facilities are difficult due to geographical location. (Staton, 2012) In February 2014, The New York Times reported that India, the second-largest exporter of over-the-counter and prescription drugs to the United States, is coming under increased scrutiny by American regulators for safety lapses, falsified drug test results, and selling fake medicines. This is important to the American consumer because India's pharmaceutical industry supplies 40 percent of over-the-counter and generic prescription drugs consumed in the United States. (Harris, 2014) In March 2014, the FDA banned imports from Indian generic manufacturer's Sun

Pharmaceutical Industries Ltd's plant at Karkhadi in the western state of Gujarat, India. (Siddiqui & Chatterjee, 2014) Although the exact reason for the ban was not cited, these recent events indicate that the drug problem, specifically quality and counterfeits, is serious.

Just as importantly, while it is possible to stop sale within the United States in the legitimate supply chain, it is very difficult to apply statutes and laws, and enforce these laws when they are jurisdictionally unenforceable. The United States has no jurisdiction in many regions of the world where counterfeit drugs are a serious problem. This situation is further complicated by the fact that counterfeit drugs present significant public-health risks, especially in less developed and third-world societies where counterfeit drugs are most prolific. In order to address this issue, the role that trade agreements play in enforcement of the goods is important. It is not always possible to apply local laws and enforcement in foreign lands where counterfeits are produced for sale locally, and methods proposed to stop the proliferation of these goods, including trade sanctions must be considered and reviewed.

CHAPTER 2. PROJECT SUMMARY

Overview

Counterfeit drugs are a problem for criminal justice. Theft of IP in the pharmaceutical industry has caused sickness and death (Newton, et al., 2006; World Health Organization, 2008; Wondemagegnehu, 1999). It is necessary that the perpetrators of these crimes are brought to justice. In some cases, threats to health and safety are short term; in others they are long term. This research describes these threats in detail.

The problem is complex, and there are many important factors that need to be considered to successfully address the problem. Public-health challenges, drug-development challenges, legal-challenges, and financial considerations are all important aspects that need to be understood. This research details these topics so appropriate solutions to the problem can be proposed.

This project is also important to forensic science. It defines the challenges faced by the field of forensic science and proposes methods that may be used to address these challenges. This will enable forensic scientists to provide support to law enforcement and other members of the legal system to successfully investigate and adjudicate these crimes.

This dissertation details and describes the integral aspects of the counterfeit-drug problem related to forensic science and the criminal justice system. It is important to start, therefore, by defining the term “counterfeit drug”. Depending upon the source, the geographic location, and the context, this term may have different meanings. For the purpose of this dissertation, a counterfeit drug is one which is deliberately and fraudulently mislabeled with respect to identity and/or source. For instance, a counterfeit VIAGRA® tablet is designed to look as if the tablet

was manufactured by Pfizer, the brand owner. The color, size, shape, and tablet markings would be such that they give the impression they are an authentic Pfizer VIAGRA tablet. Figure 1 (Hensley, 2013) shows the front and back of authentic and counterfeit VIAGRA tablets. The tablets on the left (top and bottom) are counterfeit; the tablets on the right (top and bottom) are authentic.



Figure 1. Counterfeit VIAGRA pills on the left (top and bottom) and authentic VIAGRA on the right (top and bottom).

The problem of counterfeit drugs is also significantly impacted by substandard drugs. Substandard drugs are considered in this dissertation. Sometimes with regard to drugs, the terms “counterfeit drug” and “substandard drug” are mistakenly used interchangeably. Substandard drugs include, but are not limited to, illegal imitations, expired drugs repackaged for sale, and drugs that have not been stored properly and have may have lost efficacy. An illegal imitation is a drug whose sale is in violation of government regulation (and is, therefore, illegal), but is not a counterfeit because the drug is not purported to be the brand name of the patent holder (the drug is “generic”). An example of an illegal imitation is an unregulated generic version of a drug. For instance, tablets of sildenafil citrate (VIAGRA) sold within the United States, but that do not represent themselves as being from Pfizer, the brand owner of VIAGRA, are illegal imitations.

Generic versions of VIAGRA are not legal for sale in the United States. They are “illegal”. They are “imitations” because they are not purported to be VIAGRA, but rather they imitate VIAGRA. Figure 2 shows an example of an illegal imitation. The tablet on the left is generic VIAGRA that was purchased in the United States. The “DP” marking on the tablet is not likely to be confused with the markings on the authentic VIAGRA tablet, but the product is intended to imitate the authentic VIAGRA product. It is extremely important to recognize that these definitions may be convoluted and should always be defined in context.



Figure 2. The tablet on the left is an illegal imitation (substandard) of the authentic VIAGRA tablet shown on the right.

Immediate and long-term threats to public health are the primary reason counterfeit drugs are such an important issue. The impact of counterfeit drugs on public health is described in chapter 3. Analytical challenges faced by the forensic scientist are described in chapter 4. Chapter 5 describes the values and challenges of field-portable instrumentation, while chapter 6 details the samples and sampling matrix for this research. Chapters 7 through 10 describe analytical testing performed on samples using field-portable instruments to aid in the successful investigation and adjudication of counterfeiters. Dimensional measurements, infrared spectroscopy, Raman spectroscopy, and gas chromatography-mass spectrometry (GC-MS) were all used to determine the ability of each technology to identify and source counterfeits. Chapter 11 summarizes the analytical testing by describing a proposed method and workflow for the

analytical testing of non-authentic samples in the field using portable instruments. In addition, the challenges of admissibility as evidence in United States courts of each of these technologies for this intended use in the field is presented. Chapters 12 through 16 detail the aspects of the counterfeit-drug trade that impact public health, and therefore, impact forensic science and criminal justice. It is important to describe these roles and processes so that the problem is understood and an appropriate solution can be proposed. Chapter 12 describes the drug-development process regulated by FDA. Chapters 13 and 14 describe patents and the patenting process as related to the pharmaceutical industry, including a discussion of the Hatch-Waxman Act and critical aspects relevant to IP protection and future of the pharmaceutical innovation. Chapter 15 describes ways to enforce IP rights including enforceable laws in some jurisdictions, and sanctions and trade agreements in others. Chapter 16 describes funding of pharmaceuticals. Chapter 17 summarizes the long-term challenges counterfeit drugs have on public health. This chapter will describe how counterfeit drugs will impact the future of pharmaceutical innovation. Finally, the thesis is summarized in Chapter 18. The value and contribution of this project to forensic science and criminal justice is described.

Research Questions

The research questions that were answered in this dissertation are as follows:

- (1) To what extent do counterfeit and substandard drugs present a public-health problem?
- (2) Is it possible to develop an analytical scheme to identify counterfeit drugs using field-portable instrumentation?
- (3) How will failure to protect and enforce IP rights threaten the future of pharmaceutical innovation?

CHAPTER 3. TO WHAT EXTENT DO COUNTERFEIT AND SUBSTANDARD DRUGS PRESENT A PUBLIC-HEALTH PROBLEM?

Counterfeit and substandard drugs pose immediate and long-term dangers to public health in both developed and developing societies. The immediate dangers are usually directly related to the physical and chemical composition of the drug product. In some instances, poisoning occurs from ingestion; in others, an incorrect dosage of API renders the drug ineffective or harmful. These immediate dangers may even be fatal and will be described in this chapter.

There are at least two long-term dangers counterfeit and substandard drugs pose to public health. The first is the development of resistance to drugs that results from the proliferation of counterfeit and substandard drugs; the second is the threat to pharmaceutical innovation that these goods present. The development of drug resistance will be covered within this chapter. The threat to pharmaceutical innovation is more complicated, and understanding this threat requires an understanding of matters related to criminal justice, regulatory affairs, public health, law, and science. These individual topics will be covered throughout this dissertation, and then the threat to pharmaceutical innovation will be covered in chapter 17.

Immediate Danger of Counterfeit and Substandard Drugs

The immediate dangers of the counterfeit and substandard drug problem are highlighted in the recent actions of the FDA in India. In February 2014, The New York Times reported that India, the second-largest exporter of over-the-counter and prescription drugs to the United States, is coming under increased scrutiny by American regulators for safety lapses, falsified drug test results, and selling fake medicines. This is important to the American consumer because India's pharmaceutical industry supplies 40 percent of over-the-counter and generic prescription drugs

consumed in the United States. (Harris, 2014) In March 2014, the FDA followed up this report by banning imports from Indian generic manufacturer's Sun Pharmaceutical Industries Ltd's plant at Karkhadi in the western state of Gujarat, India. (Siddiqui & Chatterjee, 2014)

These events are important for a few reasons. First, they show the importance of the issue of drug safety to regulators in the United States. Larger numbers of drugs are coming from overseas where regulators traditionally have been less strict about enforcing drug safety and other issues that would be easier to enforce locally at the point of manufacturer. For example, resources available to perform facility inspections overseas have been limited. (Food and Drug Administration, 2010; Staton, 2012) It seems, though, that the threat these goods are posing to the American consumer is becoming too great and action at this time is required. (Harris, 2014; Siddiqui & Chatterjee, 2014; Staton, 2012) Second, it shows the amount of control the FDA has to protect its regulated drug trade. Although these plants are not located within the United States, they are required to follow FDA guidelines since they will be selling their product within the United States. This is important because regulation, including enforcement, helps to bring safety, but is expensive. Cost is a factor when evaluating the problem of counterfeit drugs. Third, India supplies a large percentage of generic prescriptions to the United States market, but the amount of innovative medications coming from this region of the world is significantly lower than innovation in the United States and Europe. This is important because the cost of innovation is significantly higher than the cost of manufacturing generics. This is a very important aspect with regard to the future of pharmaceutical innovation. These details will be discussed in later chapters.

While these recent events are important and show there is a need to address the counterfeit-drug problem in the United States, there are no geographical limits to the immediate

dangers of counterfeit and substandard drugs. In fact, you are much more likely to encounter a counterfeit drug outside of the United States than you are within its borders. The record of public harm due to counterfeit and substandard drugs throughout the world is well established. Some of these instances have been summarized below.

In 2004, an otherwise healthy 22-year-old Argentinean woman being treated for a mild case of anemia died after the seventh injection of a ten-injection treatment with a toxic counterfeit iron supplement. Subsequent analysis showed that instead of iron sorbitol, the API in AstraZeneca's legitimate Yectafer®, the counterfeit samples contained a different iron derivative in a concentration three times as high as in the original product. This caused fatal liver failure. Authorities managed to prosecute several members of the counterfeit drug's distribution chain, but those who actually produced the drug were never identified or caught. (Loewy, 2007) On a larger scale, over 100 people in Panama died as a result of taking toxic counterfeit glycerin in 2006. These deaths were directly linked to a Chinese manufacturer that made and exported diethylene glycol as 99.5% pure glycerin. This toxic solution of diethylene glycol was unwittingly mixed into 260,000 bottles of cold medicine. (Bogdanich & Hooker, 2007)

Death due to the lack of the proper dosage of API in counterfeit and substandard drugs is also documented. In February 2005, a 23-year-old man presented with a fever to a rural hospital in eastern Burma where he was diagnosed as having uncomplicated hyperparasitaemic falciparum malaria by microscopy (4.2% infected red blood cells). He was treated with oral artesunate, labeled as made by Guilin Pharmaceutical (Guangxi, People's Republic of China), 4 mg/kg once a day, the treatment of choice in this region. On the third night the young Burmese man became unconscious and was transferred to another hospital where he was found to be in a coma (Glasgow Coma Score = 3/15), with renal failure and a higher parasitaemia (5.5% infected

red blood cells). He was perfused with intravenous fluids, received an injection of intravenous artesunate (2.4 mg/kg) and was transferred to a third hospital where he died within 12 hours of arrival from cerebral malaria. The amount of artesunate in the tablet was determined to be 10 mg, rather than the purported dosage of 50 mg. (Newton, et al., 2006) These authors refer to this death and others like it as manslaughter. They present as part of their evidence published research showing that artemisinin derivatives were used in this region to treat malaria, and not one of 600 patients prospectively studied with $\geq 4\%$ parasitaemia had died.

These examples resulted in immediate harm to either the patient or the public in regions outside of the jurisdiction of the United States. These counterfeit or substandard samples are either poison or ineffective and lead to harm, disease, or death. There are many more examples throughout the world, but it is important to note that in many cases, instances are not reported, or the details of the event are not reported well for various reasons. (Cockburn, Newton, Agyarko, Akunyili, & White, 2005)

In the United States, the situation is usually identified and reported more quickly than in other regions of the world. Recent events related to counterfeit versions of the drug Avastin® in the United States were reported and mitigated almost immediately. Other examples of substandard or counterfeit drugs in the United States market are usually responded to with similar expediency. (Pills for birth control seized as counterfeit, 1984; Wax, 1995)

One significant challenge to FDA regulators, though, is in management of drugs in the United States market that are the product of a global supply chain. The recent events related to more stringent control in India are evidence of this fact. (Siddiqui & Chatterjee, 2014) In addition, the inability to effectively manage this supply chain resulted in substandard versions of

the drug heparin infiltrating the highly regulated pharmaceutical market in the United States. The consequences were fatal.

In January 2008, the United States Centers for Disease Control and Prevention began a nationwide investigation of severe adverse reactions that were first detected in a single hemodialysis facility. Preliminary findings suggested that heparin was a possible cause of the reactions. (Blossom, et al., 2008) Ultimately, a total of 785 adverse-reaction reports including 81 deaths in the United States were associated with the contamination of heparin. Intensive investigations, inspections, testing, and chemical analysis related to Baxter's heparin identified a previously unknown contaminant, oversulfated chondroitin sulfate. Oversulfated chondroitin sulfate is a modified form of chondroitin sulfate and was detected in samples of heparin crude materials, heparin API's, and finished heparin drug products.

Chondroitin sulfate is a naturally occurring in animal cartilage and is often used as a dietary supplement and in supplements to treat arthritic joints. Oversulfated chondroitin sulfate, however, doesn't occur naturally and was created by chemical modification of chondroitin sulfate. The production of crude material for the production of heparin starts with the isolation of heparin from pig intestines. Many of those pigs come from rural farms in China, with the intestines initially processed at unregulated small workshops. (Labadie, 2012) During this crisis, it was found that the United States Pharmacopeia (USP) testing monograph for unfractionated heparin sodium did not detect the presence of oversulfated chondroitin sulfate in heparin. New tests and specifications have since been developed by the FDA and the USP and put in place to not only detect the contaminant oversulfated chondroitin sulfate, but also to improve assurance of quality and purity of the drug product. (Keire, et al., 2011)

Long-Term Danger of Counterfeit and Other Substandard Drugs

Drug Resistance

Counterfeit drugs also present long-term challenges to public health. They allow for the development of resistance to current medications. Frequently, this type of situation occurs in regions of the world where reports indicate that as much as, if not more than, half of prescription drugs are suspected to be counterfeits. It has been reported that counterfeit artesunate (artesunate is one of a number of drugs used for the treatment of malaria) comprises between 33% and 53% of the supply of this drug in mainland Southeast Asia. (Senior, 2008) Anti-infective medicines containing sub-therapeutic amounts of API, whether counterfeit or substandard, increase the risk of spreading resistance to the drug. (Shakoor, Raylor, & Behrens, 1997) The recent discovery of fake artesunate containing small quantities of API (Fernández, et al., 2006; Newton, Green, Fernández, Day, & White, 2006) raises the likelihood that these counterfeits will facilitate the selection and spread of *Plasmodium falciparum* parasites resistant to artemisinin derivatives. (Newton, et al., 2006)

Unfortunately, poor-quality drugs are rarely mentioned as important in the evolution of drug resistance. This is in part due to the fact that differentiating the relative roles of widespread unregulated use of inadequate anti-infectives from poor drug quality is very difficult in these geographical regions. (Newton, Green, Fernández, Day, & White, 2006) According to World Health Organization (WHO) data, malaria infected around 219 million people in 2010, killing around 660,000 of them - the vast majority in sub-Saharan Africa. Robust figures are hard to establish for a disease that affects mainly poor communities in rural areas of developing countries, and some global health experts say the annual malaria death toll could be double that. (Kelland, 2014)

Aside from malaria, other diseases are reported to develop resistance due to counterfeiting. The high prevalence of substandard chloramphenicol and cotrimoxazole in Burma could well have contributed to the high frequency of typhoid antibiotic resistance. (Shwe, Nyein, & Yi, 2002) Poor quality rifampicin and pyrazinamide (Wondemagegnehu, 1999) are also likely to be fueling the spread of multidrug-resistant mycobacterium tuberculosis. Loss of these medicines would likely lead to therapeutic failure. The need for the development of new anti-infectives is indicated, when so few new ones are being produced. (Trouiller, et al., 2001)

This observation is especially problematic when considering results of a recent study of global warming and the occurrence of malaria at higher elevations. These authors reported that future global warming could lead to a significant increase in malaria cases in densely populated regions of Africa and South America unless disease monitoring and control efforts are increased. (Siraj, et al., 2014) In a study of the mosquito-borne disease that infects around 220 million people a year, researchers from Britain and the United States found what they describe as the first hard evidence that malaria creeps to higher elevations during warmer years and back down to lower altitudes when temperatures cool. (Kelland, 2014) This in turn "suggests that with progressive global warming, malaria will creep up the mountains and spread to new high-altitude areas." (Neuhauser, 2014) People who live in these areas have no protective immunity because they are not used to being exposed to malaria, so they will be particularly vulnerable to more severe and fatal cases of infection. (Kelland, 2014)

For their study, Siraj and colleagues analyzed data from Ethiopia and Colombia, looking at malaria case records from the Antioquia region of western Colombia from 1990 to 2005 and from the Debre Zeit area of central Ethiopia from 1993 to 2005. By excluding other factors that influence malaria case numbers, such as mosquito-control programs, resistance to anti-malarial

drugs and fluctuations in rainfall, they found that the median altitude of malaria cases shifted to higher levels in warmer years and back to lower levels in cooler years. The authors purport that a clear, unambiguous signal that can only be explained by temperature changes. They state this is indisputable evidence of a climate effect. The researchers noted that their work was limited to two countries on two continents, and suggested it should be replicated in more countries with malaria in highland regions before more general trends are assumed. (Siraj, et al., 2014)

It is clear that both counterfeit and substandard drugs have a negative impact on public health and, therefore, are a problem for both the forensic scientist and other practitioners within the criminal justice system.

CHAPTER 4. FORENSIC SCIENCE AND COUNTERFEIT DRUGS

The Role of the Forensic Scientist in the Counterfeit-Drug Problem

The threat posed by counterfeit drugs to public health and safety was established in the previous chapters. These goods are manufactured and distributed by individuals and criminal organizations that need to be identified and brought to justice. (United Nations Office on Drugs and Crime, 2014) Executing this capability relies upon the practice of good forensic science. Counterfeit samples need to be identified using methods of analysis that are admissible in court. Classification of these samples provides useful information that may be used in an investigative manner to establish provenance and identify counterfeiting groups or organizations. It is important that this capability be performed in the field so that decisions about a sample's authenticity may be made without delay. Frequently and for various reasons, counterfeit drugs are sold in foreign countries distant from their manufacture site. (Dean, 2013) If a Customs agent were able to rapidly and reliably establish authenticity, the import of these goods to the target nation could be denied before infiltration of these illicit goods into the local supply chain occurs.

Literature Review with Regard to Analytical Testing of Counterfeit Goods

A review of the scientific literature shows that a method to routinely identify counterfeit drugs has not been described. In addition, although attempts were successful in some specific instances, a method for the routine analysis of counterfeit goods or drugs to determine provenance is yet to be established. Finally, there is a lack of discussion in the literature with regard to the analysis of counterfeit goods in the field. Virtually all of the literature describing counterfeits references lab-based methods. Most are used to detect, identify and quantify the API. From this information, provenance determinations are attempted. The ingenuity, especially

for counterfeit drugs, is in the details of the instrumentation or methods used for sample introduction rather than in the approach used to address the counterfeit-drug problem.

A search of the term “counterfeit” in the electronic databases of the Journal of Forensic Sciences and Forensic Science International for the years 1983 through March 2014 returned 76 and 78 articles, respectively. In more recent years, the frequency of articles has increased, indicating this type of analysis is becoming more prevalent. Figure 3 shows the frequency of occurrence of the term “counterfeit” between the years 1995 and 2013. This data shows an increased interest by forensic scientists in the analysis of counterfeits as physical evidence in the past few years. Interestingly, the type of evidence analyzed ranges from tobacco used to pass off counterfeit cigarettes, to high-end designer drugs intended to circumvent both IP rights and government regulation.

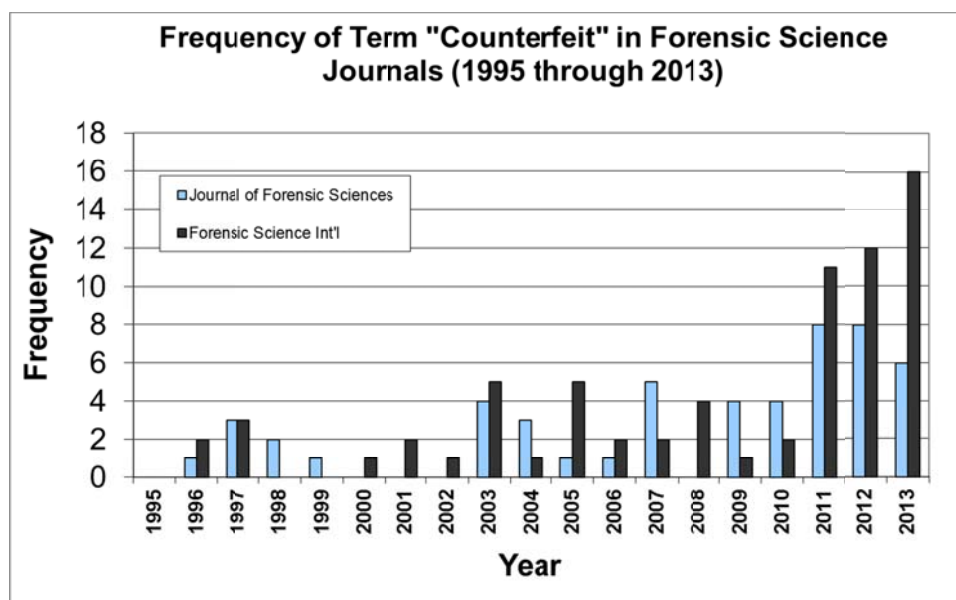


Figure 3. Frequency distribution of the term “counterfeit” in forensic science journals.

Acampora, Ferranti, Malorni & Milone analyzed pigments in a counterfeit bank note using direct-mixture-analysis mass spectrometry. Pigments identified in the note were the same

pigments contained within ink samples suspected to be used to produce the notes. The conclusion drawn by the authors was that the bank note was consistent with being made using inks from the suspect sample, but no attempts were made to individualize the inks to the bank notes. (Acampora, Ferranti, Malorni, & Milone, 1991) Hida, Mitsui and Minami performed x-ray fluorescence (xrf) and microscopy to analyze counterfeit coins. The counterfeit coins tested, just like the authentic coins, were comprised primarily of copper and nickel. The amount of copper and nickel present was higher in the counterfeit coins. In addition, the authors noted that chromium, manganese, iron, nickel, and zinc profiles of the counterfeit coins were quantitatively more variable than what was observed in the authentic coins. (Hida, Mitsui, & Minami, 1997) Hida, Sato, Sugawara and Mitsui described analysis of counterfeit coins using xrf and x-ray diffraction (xrd). Using statistical methods, these authors were able to cluster the coins into three groups. One group included 250 counterfeit coins, the second group included 27 counterfeit coins and the third group included the four authentic coins analyzed. (Hida, Sato, Sugawara, & Mitsui, 2001) This same year, Hida and Mitsui described xrf testing of prepaid turnpike and subway cards. They developed a multivariate statistical method to categorize 200 authentic subway cards into at least four different groups. This same method was then applied to 20 counterfeit turnpike cards, as well as 12 authentic turnpike cards. Using this multivariate statistical method, this group of 32 cards was divided into three groups. One was comprised of the 20 counterfeit cards plus one authentic card; the other 11 authentic cards were divided into two groups. (Hida & Mitsui, 2001) Bartle and Watling used laser ablation-inductively coupled plasma-mass spectrometry (LA-ICP-MS) to analyze the isotope distribution profiles of porcelain. From this work, they concluded that LA-ICP-MS can be used to identify and classify Oriental porcelains and establish their origin of country. They furthered their conclusion by stating that

minor variations in the spectral fingerprints of porcelains from the same country can be attributed to variations in production methods both over time and between individual potters. This indicated to them a potential to further provenance Oriental porcelains to specific production kilns. (Bartle & Watling, 2007) Sugawara used polarized infrared radiation to differentiate counterfeit Japanese passports from authentic samples. When unpolarized radiation was used, the authentic samples were indistinguishable from the counterfeits. When polarized radiation was used, however, peak ratios were used for successful differentiation. (Sugawara, 2007) Sugawara also successfully applied confocal-type laser microscopy to Japanese passports with the goal of differentiating authentic samples from counterfeits. (Sugawara, Passport examination by a confocal-type laser profile microscope, 2008) Suzuki used the acoustic characteristics of 500-yen coins to differentiate authentic coins from counterfeits. The author concluded that this simple and rapid technique can not only be used to differentiate authentic from counterfeit coins, but also that the method may be applied to the classification of counterfeit coins if databases of coins were developed. (Suzuki, 2008) LaPorte and colleagues used microscopy to analyze the printing defects in envelopes. These authors concluded that their study corroborates previous assertions that assessments to determine whether two or more items may have a common origin can be based upon the evaluation of printing defects. (LaPorte, Stephens, & Beuchel, 2010) Pérez-Bernal and colleagues performed principal component analysis (PCA) on metallic distribution data from the ash of tobacco from different brands and types of cigarettes. This data indicates it may be possible to use this type of analysis to assess the brand of tobacco used for manufacture of cigarettes. These authors state that a limitation of their study is in the number of different types of tobacco analyzed, as well as in the number of different brands of cigarettes analyzed. (Pérez-Bernal, Amigo, Fernández-Torres, Bello, & Callejón-Mochón, 2011) Romão et

al. used electrospray ambient ionization-mass spectrometry (EASI-MS) and showed this technique may be successfully applied as a fast and non-destructive screening tool for documents, specifically for Brazilian vehicle registration. (Romão, et al., 2012) Brzezinski and Craft summarized analysis performed on seized samples of counterfeit toothpaste. These samples were analyzed to determine the number of microorganisms present. Although the authors showed the samples contained high numbers of microorganisms, they were not able to assign all samples to either a manufacturing site or method of manufacture. (Brzezinski & Craft, 2012) Cao, Gao, Fan, and Yan presented an automatic and efficient detection algorithm for copy-move forgery for digital counterfeits. (Cao, Gao, Fan, & Yang, 2012) Nam and colleagues used liquid chromatography-mass spectrometry-mass spectrometry (LC-MS-MS) to detect corticosteroids in cosmetic creams. The method allowed for the analysis of large numbers of samples in a short period of time. As a result of this work, illegal steroids were detected in four different cosmetic products and resulted in these products being withdrawn from local markets. (Nam, Keun, Lee, & Lee, 2012) Božičević and colleagues used micro Raman spectroscopy to identify a common origin of toner-printed counterfeit banknotes. Their results show that micro-Raman spectroscopy can be successfully applied as a method for the analysis of color toner printed counterfeits, such as banknotes and documents, in some instances. (Božičević, Gajović, & Zjakić, 2012). Baechler and colleagues applied chemometric methods to data from visual markers to classify false identity documents. Their method generated low error rates and was concluded to be able to link documents to a common source or to differentiate them. (Baechler, et al., 2013)

With regard to the analysis of counterfeit drugs, most of the literature relevant to the field of forensic science describes methods and techniques for the identification and/or quantitative

analysis of the API and other ingredients present in the counterfeit drug. Alabdalla discussed the analysis of counterfeit samples of Captagon®, a drug product containing the API fenethylline, using GC-MS. This drug is commonly abused in the country of Jordan and throughout the Middle East. The author concluded that the comparison of chromatographic patterns is useful in establishing links between samples under investigation. In addition, the author concluded that profound similarities of chromatographic profiles support the assumption that samples could have a common origin, or at least have been produced by the same manufacturer. (Alabdalla, 2005) Baer, Gurny, and Margot used near-infrared (NIR) analysis to evaluate cellulose and lactose. Although they state it may be possible to use this type of analysis to source ecstasy tablets, their data is preliminary and the intra- and inter-variability of compression batches using this method is unknown. (Baer, Gurny, & Margot, 2007) Soltaninejad and colleagues discussed the analysis of counterfeit buprenorphine using GC-MS and liquid chromatography (LC) with a diode array detector. These authors showed that the counterfeited samples analyzed were derived from illicit heroin. Due to the therapeutic and metabolic differences between buprenorphine and heroin derivatives, the authors concluded that the use of counterfeit buprenorphine leads opiate abusers to serious health risks. (Soltaninejad, Faryadi, Akhgari, & Bahmanabadi, 2007) Venhuis, Blok-Tip and de Kaste used high-performance liquid chromatography (HPLC) with a diode-array detector fitted with a mass spectrometer (MS) detector to analyze three different types of seized natural aphrodisiacs. All three types of samples contained analogs of prescribed erectile dysfunction drugs. Although there was nothing unusual about the analysis, this study is interesting because these drugs were likely designed to circumvent patents by using unpatented analogs. In addition, they are being used as natural supplements and, therefore, were also likely designed to circumvent regulatory

requirements. (Venhuis, Blok-Tip, & de Kaste, 2008) Been et al. used NIR and Raman to propose a strategy for the classification of counterfeit medicine. (Been, Roggo, Degardin, Esseiva, & Margot, 2011) Kauppila and colleagues purport the use of desorption atmospheric pressure photoionization-mass spectrometry (DAPPI-MS) as a screening tool for drug samples. A primary advantage of the DAPPI-MS technique compared with GC-MS is speed. Their research showed the DAPPI-MS technique could be used to identify controlled substances within drug samples within seconds. (Kauppila, et al., 2011) Lopatka and Vallat evaluated surface granularity of tablets to differentiate different samples from each other. They purport that this type of analysis contains valuable information with regard to production batch identity. (Lopatka & Vallat, 2011) Samms et al. used direct-analysis-in-real-time – time-of-flight – mass spectrometry (DART-TOF-MS) to analyze street samples of Xanax®. The authors propose this as a new method to identify API's. (Samms, Jiang, Dixon, Houck, & Mozayani, 2011) Jung et al. propose a method for quick and reliable identification of counterfeit VIAGRA® and Cialis® using image processing and statistical analysis. Although this method seems useful, one of the concerns about the technique is that there is potential for a large number of false positives if tablet discoloration occurs. (Jung, Ortiz, Limberger, & Mayorga, 2012) Logan and colleagues used a variety of techniques including thin-layer chromatography, GC-MS, HPLC, and liquid chromatography – time-of-flight – mass spectrometry (LC-TOF-MS) to characterize a variety of different types of samples including counterfeits. It is important to note that no counterfeit samples analyzed as part of this study contained any active ingredient. (Logan, Reinhold, Xu, & Diamond, 2012) Park and Ayn summarized quantitative analysis of sildenafil and tadalafil using high-performance liquid chromatography-ultraviolet spectroscopy (HPLC-UV) analysis performed on counterfeit drugs seized in Korea. One hundred five samples were analyzed.

More than half contained more than the prescription dose of sildenafil and tadalafil. (Park & Ahn, 2012) Patterson et al. developed and described an electrospray ionization-liquid chromatography-mass spectrometry (ESI-LC-MS) analytical method used to differentiate sildenafil from its vardenafil analog. This work is valuable because these compounds are difficult to differentiate using more common MS methods due to similarity in the fragmentation patterns of the two compounds when analyzed using a quadrupole MS. (Patterson, Mabe, Mitchell, & Cory, 2012) Ortiz et al. used attenuated total reflection (ATR) Fourier-transform infrared spectroscopy (FT-IR) with PCA analysis to classify seized samples of Cialis and VIAGRA. The PCA applied to ATR-FTIR data allowed grouping samples according to their different chemical profiles, distinguishing successfully between authentic and counterfeit samples. In addition, PCA scores inserted counterfeit drugs from different seizures in the same cluster, suggesting a common illicit source for these medicines. (Ortiz, et al., 2013) Mariotti and colleagues evaluated the trends in counterfeit amphetamine-type simulants after prohibition of these goods in Brazil. These authors concluded that visual inspection and the physical characteristics like average mass were useful in indicating forgery. However, they stated that this analysis is limited and alone these measurements were not reliable to distinguish between authentic and counterfeit samples. For some samples they recommended additional analysis using GC-MS. For others they recommended other methods including PCA of ATR-FT-IR data. (de Cássia Mariotti, Ortiz, Sousa, Fröhlich, & Limberger, 2013) Ortiz and colleagues used chemometrics applied to UPLC-MS to analyze counterfeit samples of drugs used to treat erectile dysfunction. (Ortiz, et al., 2013) Anzanello et al. proposed a framework for selecting the analytical techniques providing the most conclusive data for categorizing seized drugs into authentic and unauthentic classes. With regard to VIAGRA and Cialis, these authors proposed

the use of data from UPLC–MS, physical dimensions, and ATR FT-IR. (Anzanello, Ortiz, Limberger, & Mariotti, 2014)

This literature review shows that there is a need for an analytical scheme to rapidly and reliably identify counterfeit drugs and establish provenance using methods of analysis that work well. Infrared, Raman, and gas chromatography-mass spectrometry (GC-MS) are methods that are routinely used to physically and chemically characterize drugs and drug products.

Investigation of these methods for this use is proposed. Ideally, this scheme would be applied using field-portable instruments in order to rapidly and reliably identify these goods at their port of entry. The scope of this dissertation includes an attempt to establish such an analytical scheme using field-portable instrumentation. Ultimately, the data collected in the field should be used to create a database of counterfeit drugs analyzed in order to provide forensic scientists the data they need to be able to effectively establish sample provenance.

CHAPTER 5. TESTING IN THE FIELD: PORTABLE ANALYTICAL INSTRUMENTATION

Design, Performance, and Implementation of Field-Portable Instruments

It seems appropriate to start this chapter by describing the current state of field-portable instrumentation. It is important that detection and identification of counterfeit drugs is performed in the field using methods of analysis that are rapid and reliable. At Customs check points, the ability to detect and identify these goods quickly and accurately will prevent them from entering the local supply chain. It is not always practical or possible to delay entry of cargo to wait on results of lab testing. In fact, border agents typically will only have a few minutes to make a go/no-go decision at checkpoints under conditions of high stress. (Pomfret, 2006) If detection and identification can occur in the field, law-enforcement organizations may take immediate action to prevent the infiltration of these goods into the market. It may also help to identify counterfeiters, establish provenance, and appropriately adjudicate these cases. Significant developments have resulted in the availability of smaller, lighter, and faster instruments. (Carrabba, Spencer, Rich, & Rauh, 1990; Lammert, Rockwood, Wang, & Lee, 2006; Overton, 2010; Reffner & Martoglio, 1995) In many cases, technology advances have led to the availability of handheld measuring devices and spectrometers such as infrared and Raman systems. (Smiths Detection, 2014; Wasatch Photonics, 2014) In the case of GC-MS, portable instruments are available that weigh less than 35 pounds. (Smiths Detection, 2014) These handheld and portable instruments are smaller and lighter, but yet generate data that is qualitatively comparable to data from laboratory instruments. There are, however, differences in design, performance criteria and implementation between portable and lab-based instruments.

With regard to design, field portable instruments need to be small, light, rugged, and easy to use. These systems may be hand carried to the site where analysis will be performed. Large

and heavy instruments are not practical or acceptable for this application. They are expected to experience significant wear and tear during transit and at the analysis scene. Frequently, specifications for drop testing and other ruggedization criteria are as critical as the specifications for the signal-to-noise ratio of the spectrometer. Due to the sometimes-precarious environments in which these instruments are expected to perform, they must have an easy-to-use software interface which generates results-driven answers rather than spectral displays requiring significant user interpretation. Automatic library searching using algorithms tailored to optimize results in the field are a significant aspect of these instrument designs. In addition, sampling and other accessories are sometimes required, but are not desirable. The more complex a field-portable instrument becomes, the less likely it will become a part of the routine on-scene work flow. There is also a need to minimize impractical consumables. The more gear that needs to be carried to make an instrument perform, the less likely the instrument will be successful in the field.

Performance criteria of field-portable instrumentation, as previously stated, typically include specifications for analytical performance as well as for size, weight, and ruggedization. Specifications for analytical performance such as signal-to-noise ratio, sensitivity, and levels of detection and quantitation will be less stringent than they are for lab-based instrumentation of equivalent technologies. However, instruments will be specified to perform under much more extreme environmental conditions than lab-based equivalents. For instance, specifications may be included for performance in cold and hot temperatures, in rainy environments, or even desert-like conditions. Field-portable instruments are expected to be drop resistant and specifications allow for post-analysis decontamination. This is a significant factor for instruments intended to

be used to detect chemical warfare agents and other toxic chemicals that may be harmful to future users of the instrument.

Ease of implementation of field-portable instruments is also a significant consideration. Training requirements should be minimal. Frequently, the goal is to have non-scientists use field-portable instruments. This translates to a need to minimize modes of operation, simplify user interfaces, and generate results-driven answers. Electronic libraries and the search algorithms used to search these databases of spectra are a critical factor when considering the potential success of a field-portable instrument. This is because users in the field do not usually have the time available at the scene, or the practical experiences required to process and interpret complicated data files. It is common for field-portable instruments to use library-search algorithms designed to identify mixtures rather than use an algorithm like correlation coefficient which assumes pure samples. The ability of the user to separate a mixture sample in the field prior to analysis are sometimes limited, so designing the library-search algorithms to compensate for this issue during data processing adds value to these systems. In many ways, field portable instruments are only as useful out in the field as the success of their library-search algorithms, and the size and quality of the library searched.

Technologies Evaluated in this Study

As part of this research, analysis in the field was performed using portable infrared, Raman and GC-MS spectrometers.

Attenuated Total Reflection Infrared Spectroscopy

Most field-portable mid-infrared systems that are used for rapid analysis in the field perform ATR measurements. This method of infrared analysis is useful in field applications

because it requires little-to-no sample preparation. In addition, ATR spectra are very reproducible, which is also useful for field applications.

Attenuated total reflection occurs when a sample is brought into contact with an internal-reflection element (IRE) that has a higher refractive index than the sample. The IRE is also referred to as an ATR crystal. Typical IREs are ZnSe, diamond, and germanium. ZnSe and diamond have refractive indices of 2.4; germanium has a refractive index of 4.0. If radiation is brought through the IRE at an angle greater than the critical angle, the beam will be totally internally reflected.

The critical angle (ϕ_c) between two media with different indices of refraction (n_1 and n_2) is defined by the angle whose sin is n_1/n_2 :

$$\phi_c = \arcsin \frac{n_1}{n_2} \quad \text{Equation 1}$$

For ATR spectroscopy, $n_1 < n_2$. A critical angle exists only for radiation traveling through a higher-index medium into a lower-index medium. At angles greater than the critical angle, the incident radiation is completely reflected, but there is an electromagnetic field that extends beyond the IRE. This field's strength decreases as the distance from the IRE surface increases; it is referred to as an evanescent wave. It follows that if an absorbing material is brought into contact with the IRE, the evanescent wave will be absorbed at wavelengths where the material has an absorption band, and the amount of energy reflected back through the IRE will be attenuated.

The distance the evanescent wave extends past the crystal surface and into any sample in contact with the surface can be defined in terms of the depth of penetration. The depth of penetration (dp) is defined as

$$dp = \frac{\lambda}{2\pi(n_1^2 \sin^2 \theta - n_2^2)^{\frac{1}{2}}} \quad \text{Equation 2}$$

where λ is the wavelength of radiant energy, n_1 is the index of refraction of the IRE, n_2 the index of refraction of the sample, and θ the angle of incident radiation on the interface. This depth of penetration may essentially be considered the sampling depth. (Reffner & Martoglio, 1995)

Assuming contact between the IRE and the sample is made, the sampling depth is consistent from measurement to measurement. For field analysis, this is very useful because it makes it easier to collect reproducible spectra which can be easily compared with library spectra for comparison and identification. It is important to recognize, though, that transmission spectra are not wavelength dependent. Therefore, comparisons between ATR and transmission spectra should allow for expected differences.

As part of this study, tablet cores were analyzed using a field-portable FT-IR ATR spectrometer with a diamond IRE. In the system used, the diamond sampling area is 1.3 mm x 0.8 mm. Less than 1 mg of sample was pressed against the diamond for analysis. The optical engine is designed with a resistively heated wire source, a fiber optic laser diode reference, cube-corner reflectors, and a thermo-electrically cooled deuterated L-alanine doped triglycine sulfate (DLATGS) detector. Cube-corner reflectors are mounted on two arms of a double pendulum modulator driven by an electromagnetic actuator. Interferograms are collected by sweeping the reflectors over the required optical path difference. A schematic of this interferometer is shown in figure 4. Both reflectors move synchronously so each reflector travels half the linear distance required in a traditional Michelson interferometer. This optical engine is advantageous in field-portable systems because of its tilt compensation, reduced motion, inherent self-alignment and

disturbance rejection. (Arnó, et al., 2013) Although the system includes automatic library-searching capabilities, no library-searching functions were used in this study.

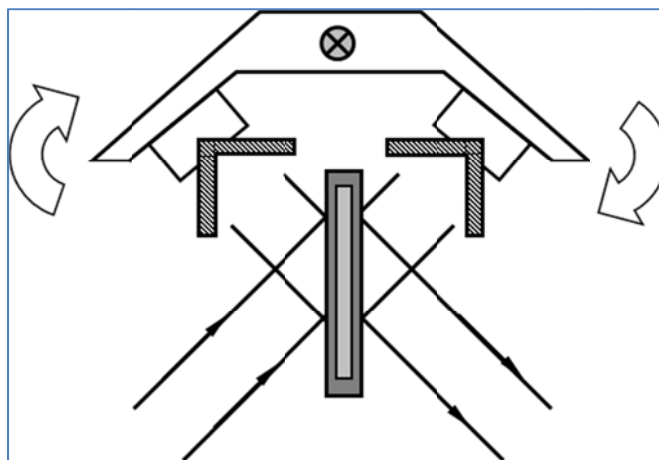


Figure 4. Schematic of corner-cube interferometer. Photo courtesy of Mike Frunzi and Dustin Levy, Smiths Detection, Danbury, CT.

Raman Spectroscopy

The Raman spectrometer used for these experiments uses a volume phase holographic (VPH) grating to optimize signal. The use of holographic filters in Raman spectrometers is one of the primary reasons Raman spectrometers were capable of becoming field portable.

The first reported use of holographic in Raman spectrometers was by Carrabba et al. in 1990. The filter was used for Rayleigh-line rejection in Raman spectroscopy. (Carrabba, Spencer, Rich, & Rauh, 1990) The use of these filters was a significant advance because the ability to reject the elastic scattering meant that any size monochromator could be used to collect Raman spectra. Depending on the type of filter produced, and how it is mounted, lines as close as 30 cm^{-1} from the laser line can be observed. (Adar, Delhay, & DaSilvia, 2003).

When a beam of electromagnetic radiation impinges upon on a particle that is small with respect to the wavelength of the radiation, the electrons of the particle are in an intense,

alternating field caused by the electric and magnetic components of the radiation. During this interaction, the electrons of the particle oscillate with the same frequency of the incident radiation and thereby produce electromagnetic radiation of the same frequency as the incident radiation, but emanating from the particle in all directions. This appears to be scattered radiation and is referred to as Rayleigh scatter. If, however, the polarizability of the particle, usually a molecule, changes rather than remains constant, then the intensity of the scattered radiation varies accordingly. Polarizability is related to the ease of separation of charges in an external electrical field. If one or more normal modes of vibration of a molecule involve changes in the polarizability, then the scattered radiation contains this vibrational frequency superimposed upon the frequency of the incident radiation. This is the Raman effect. For a vibration to be active in the Raman effect, the polarizability of the molecule must change during the vibration. Most collisions of the incident photons with the sample molecules are elastic, or Rayleigh. Raman scatter is significantly weaker than Rayleigh scattering. (Willard, Merritt Jr., Dean, & Settle Jr., 1988) The use of lasers to generate sufficient Raman signal, coupled with holographic filters to reject Rayleigh line scatter enabled significant advances in Raman instrumentation and the field portability of these instruments.

Classical electromagnetic theory predicts the Raman effect, although a quantum mechanical treatment is needed for detailed explanation. According to classical theory, the polarization, P , expressed as dipole moment per unit volume, is given equation 3

$$P = \alpha E \quad \text{Equation 3}$$

where E is the magnitude of the electric vector of the electromagnetic field that acts on the molecule and α , the polarizability, is the proportionality constant. Since the magnitude of the

electric vector of the electromagnetic field varies with time, t , in a sinusoidal manner, E is calculated in accordance with equation 4

$$E = E_0 \cos 2\pi \nu t \quad \text{Equation 4}$$

and the polarization becomes

$$P = \alpha E_0 \cos 2\pi \nu t \quad \text{Equation 5}$$

The polarizability consists of two parts: α_0 , the polarizability when the atoms of a molecule are in their equilibrium positions, and a second term that is the sum of the polarizabilities of the molecule due to the various rotational and vibrational motions. Each term of this second part varies with the frequency associated with the particular rotation or vibration. Thus,

$$\alpha = \alpha_0 + \sum \left(\frac{\delta \alpha_n}{\delta r} \right) r_n \cos 2\pi \nu_n t \quad \text{Equation 6}$$

where α_n is the polarizability associated with the n th rotational or vibrational mode and the r_n is the maximum displacement of the involved atoms. Combining equations 5 and 6, the polarization becomes

$$P = E_0 \alpha_0 \cos 2\pi \nu t + E_0 \sum \left(\frac{\delta \alpha_n}{\delta r} \right) r_n \cos 2\pi \nu_n t \cos 2\pi \nu t \quad \text{Equation 7}$$

which may be expressed

$$P = E_0 \alpha_0 \cos 2\pi \nu t + \frac{1}{2} E_0 \sum \left(\frac{\delta \alpha_n}{\delta r} \right) r_n \{ \cos 2\pi (\nu - \nu_n) t + \cos 2\pi (\nu + \nu_n) t \} \quad \text{Equation 8}$$

The first term has the frequency of the incident radiation and is the Rayleigh scattering. The second term is the basis for the Raman effect and represents both the Stokes ($\nu - \nu_n$) and anti-Stokes ($\nu + \nu_n$) Raman bands. As previously mentioned, most collisions of the incident photons with the sample molecules result in Rayleigh scatter. Only a small portion of the excited

molecules (10^{-6} or less) may undergo changes in polarizability during one or more of the normal vibration modes, i.e., the Raman effect. Therefore, holographic filters and their ability to reject Rayleigh-line scatter are a significant advancement.

For their experiment, Carrabba et al. used holographic Bragg diffraction (HBD) filters designed for laser-line rejection at 514.5 nm. The technique for fabricating the HBD filters is based upon recording of a hologram in a dichromate gelatin/polymer graft emulsion approximately 20- μm thick between transparent plates. During the recording process, a standing-wave pattern generates a set of interference fringes which are recorded in the holographic emulsion as successive planes of high and low refractive index. The planes are separated by $\lambda/2$, where λ is the wavelength of the recording light in the medium. When used as a filter, only those wavelengths fulfilling the Bragg condition will be diffracted, while other wavelengths will be transmitted. In this way, the filter diffracts at the same wavelength at which it was recorded, if recording is carried out at normal incidence. The holographic images exhibit nearly ideal physical properties. (Carrabba, Spencer, Rich, & Rauh, 1990)

The Raman spectrometer used in this research employs a built-in 785-nm laser with $f\#1.3$ numerical aperture (NA) and volume phase holographic (VPH) grating. The detector used was a back-thinned silicon array CCD with low-noise electronics. There are some advantages to this portable system. The built-in laser with $f\#1.3$ NA enables high throughput with minimal loss of efficiency. The VPH grating allows for high diffraction efficiency, minimizes polarization effects, and is optimized over a broad range of wavelengths (although there may be a tradeoff between maximizing the bandwidth and maximizing the peak efficiency). (Baldry, Bland-Hawthorn, & Robertson, 2004) Rather than having surface structure as in classical gratings, VPH gratings diffract light by refractive index modulations within a thin layer of

material sandwiched between two glass substrates. Figure 5 shows a schematic (Kaiser Optical Systems, Inc., 2014) of a conventional grating compared with a VPH grating.

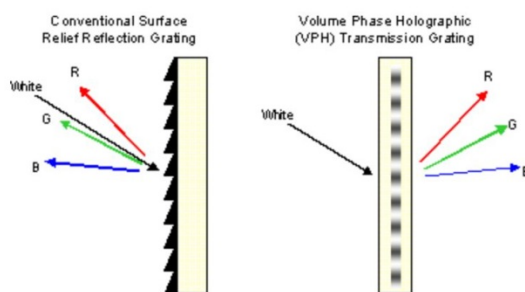


Figure 5. Schematic of diffraction from conventional and VPH gratings.

The intensity of the refractive index modulation and the depth of the grating layer are critical parameters in the performance of the grating. Light is diffracted at angles corresponding to the classical grating equation as a function of the incident angle and the frequency of the index modulation at the surface of the grating. The diffraction efficiency, however, is a strong function of the relationship between the angle of incidence and angle of diffraction with respect to the fringes formed by the refractive-index modulations within the volume of the grating. If these relationships satisfy the Bragg condition, which also depends on the depth of the grating volume and on the intensity of the grating fringes, then high peak diffraction efficiencies, approaching 100%, are possible. (Barden, 1998)

As part of this study, tablet cores were crushed in a mortar and pestle and approximately 25 mg was transferred to a glass vial. The sample was analyzed using the Raman spectrometer through the glass to evaluate chemical composition. The resulting Raman spectrum may also be sensitive to solid-form differences. Although approximately 25 mg of sample is present in the vial, the analysis spot size was approximately 50 μm for each spectrum collected.

Gas Chromatography-Mass Spectrometry

As part of this study, tablets were analyzed using a field-portable GC-MS to evaluate organic volatiles and solvents remaining in the tablet after production (residual solvents). The portable system used employs a low-thermal-mass (LTM) resistively heated capillary column directly linked with a miniaturized toroidal ion-trap MS. This design is advantageous in field-deployed settings for a few reasons. The LTM GC column enables fast separation and thermal recovery (approximately five minutes between the start of two consecutive injections). This rate of thermal recovery is achieved because only the capillary column of the GC is heated during the analysis. The miniaturized toroidal ion-trap MS minimizes power and vacuum requirements, making the technology amenable for field analysis.

Ion-trap MS systems, by virtue of their simplicity, are ideal candidates for miniaturization. They are inherently small and have only a few ion optic elements that do not require highly precise alignment compared with other types of mass analyzers. The operating pressure for ion traps is higher than for other forms of MS, allowing for less stringent pumping requirements. Furthermore, since the radio frequency (rf) trapping voltage is inversely proportional to the square of the analyzer radial dimension, a modest decrease in analyzer size results in a large reduction in operating voltage and, hence, lower power requirements. (Lammert, Rockwood, Wang, & Lee, 2006) A primary challenge for ion traps, especially when maximizing reduction in size, is the management of ion-ion repulsions in the trap. The toroidal-ion-trap design increases trapping volume and, therefore, minimizes these ion-ion repulsions.

The toroidal ion trap can be viewed as a conventional three-dimensional ion trap cross section that has been rotated on an edge through space. Figure 6 shows the geometry of the conventional ion trap with axis of rotation shown in red (left), and the toroidal ion trap with axis

of rotation shown in blue (right). As can be seen, the result of this edge rotation is a trapping field that is in the shape of a torus. This toroidal rf ion-trap design maintains a given trapping field radius while increasing the ion storage volume of the ion trap. (Lammert, Plass, Thompson, & Wise, 2001) This capability is significant.

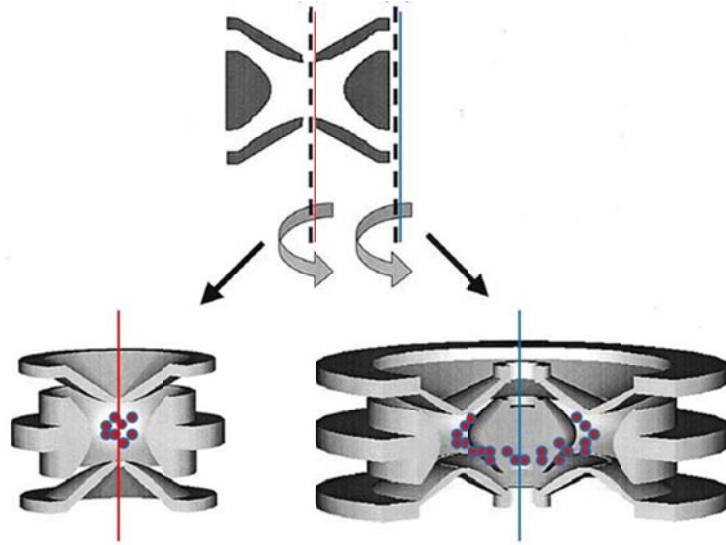


Figure 6. Cross section of conventional ion trap (left) and toroidal ion trap (right). The axis of rotation is shown as a colored line for each trap design

Equation 9 governs mass stability in a quadrupole ion-trap MS, where q is one of the two Mathieu stability parameters, r_0 is the radial dimension, V is the operating voltage, z_0 is the axial dimension, m is the ion mass, and Ω is the rf frequency. (Lammert, Rockwood, Wang, & Lee, 2006)

$$q = \frac{-8 * e * V}{m * (r_0^2 + 2z_0^2) * \Omega^2} \quad \text{Equation 9}$$

The ability to maintain the same radius, while increasing the trapping volume, gives the advantages of minimizing ion-ion interactions while working at lower voltage and, therefore,

power requirements. The ability to operate at higher pressures, as well as the reduction in power requirements are the primary advances that enabled field portability.

In this study, tablets were gently crushed and then heated in a vial for headspace analysis. Gases and volatiles in the headspace were sampled using solid-phase microextraction (SPME). Samples were thermally desorbed from the SPME upon injection into the GC-MS system. Fast separation (less than three minutes) was performed on the GC. Analytes eluted directly from the column into the ionization chamber of the toroidal ion-trap MS. An rf trapping field was applied, and resonance ejection was achieved by applying a voltage of known frequency to the filament end cap and increasing the amplitude of the rf trapping field such that the frequency of the ion becomes the same as that applied to the end cap (mass-selective instability scan). Dynamic-ionization optimized the number of ions in the trap for each analyte. Dynamic ionization control is a feature that adjusts the filament current in real time to optimize the number of ions being generated. This prevents space charging and other problems that result from overload of the ion trap. The resulting scanned mass range was from 42 to 500 m/z.

Chemometric Methods

When collecting large amounts of chemical data, it can be useful to apply mathematical methods to extract useful chemical information. As part of this research, the chemometric methods of PCA and canonical variate analysis (CVA) were applied to both the infrared and Raman data after autoscaling to investigate the classification and discrimination power of each of these methods. The deconvolution data, specifically the peak positions and areas, also were analyzed using hold-one-out cross validation (HOO-CV) PCA-CVA to determine an estimated error rate for the classification of sildenafil citrate tablets using each of these methods.

As previously stated, data was autoscaled prior to PCA analysis. Autoscaling is the combination of mean centering and variance scaling. Mean centering is performed by calculating the average data vector of all n rows in a data set and subtracting it point by point from each vector in the data set. Graphically, mean centering corresponds to a shift in the origin of the plot. Variance scaling is the process of normalizing each column so that the sum of squares equals one. Variance scaling is performed in order to give equal weight or importance to all variables (or wavenumbers) in the measured data set, and must be completed after mean centering. (Varmuza & Filmözer, 2009)

Principal Component Analysis

PCA is a chemometric method that reduces the dimensionality of data based upon the variance in the data. This allows the user to remove the large amounts of data that contain the least amount of variance. As part of this research, the number of starting dimensions was equal to the number of wavenumber data points for each spectrum. For the infrared data, the number of original dimensions was 1425; for the Raman data, the number of dimensions was 938. Of course this is a highly redundant representation and should be reduced in dimension. (Petraco, 2014)

The first PC, i.e., first reduced dimension, is the linear combination of the original variables with maximum variance. The second PC is the linear combination that exhibits the second greatest amount of variance, but is orthogonal to the first PC. Each successive PC exhibits less variance than the one before it. The linear combination of the original variables is used to form a set of derived variables, i.e., PC's. The matrix form of these derived variables is

$$Z_{PC} = X A_{PC}^T \quad \text{Equation 10}$$

where the superscript T represents the transpose of \mathbf{A}_{PC} . The new data set Z is derived from the original variables, but sorted in order of decreasing variance so PC's containing minimal information can be removed. This allows for the reduction in the number of derived variables used without the loss of a significant amount of information from the data. (Varmuza & Filmozer, 2009)

The matrix \mathbf{A}_{PC} is computed by diagonalizing the $p \times p$ maximum likelihood covariance matrix (\mathbf{S}) of \mathbf{X}

$$\mathbf{S} = \frac{1}{n-1} \sum_{i=1}^n (\mathbf{X}_i - \bar{\mathbf{X}}) \otimes (\mathbf{X}_i - \bar{\mathbf{X}}) \quad \text{Equation 11}$$

where \otimes is the Kronecker product of vectors.

Canonical Variate Analysis

For this research, CVA was performed on the derived data computed from PCA. CVA uses a covariance matrix, $\mathbf{W}^{-1}\mathbf{B}$, to find the direction of best group separation. The analysis is based on the relationship between-group (\mathbf{B}) variance and within-group (\mathbf{W}) variance.

The CVs, \mathbf{A}_{CV} , and their eigenvalues, $\mathbf{\Lambda}_{CV}$, are computed by diagonalizing the covariance matrix ($\mathbf{W}^{-1}\mathbf{B}$), where

$$\mathbf{B} = \sum_{i=1}^k n_i (\bar{\mathbf{X}}_i - \bar{\mathbf{X}}) \otimes (\bar{\mathbf{X}}_i - \bar{\mathbf{X}})^T \quad \text{Equation 12}$$

and

$$\mathbf{W} = \sum_{i=1}^k \sum_{j=1}^{n_i} (\bar{\mathbf{X}}_{i,j} - \bar{\mathbf{X}}_i) \otimes (\bar{\mathbf{X}}_{i,j} - \bar{\mathbf{X}}_i)^T \quad \text{Equation 13}$$

The non-singular \mathbf{W} is inverted using a standard inversion method. X_{ij} represents the j^{th} absorbance response in the i^{th} spectrum and \bar{X}_i is the average of all of the spectra in the i^{th} sample. There are n_i spectra in sample i . The eigenproblem for CVA is

$$W^{-1}BA_{CV}^T = A_{CV}^T\Lambda_{CV} \quad \text{Equation 14}$$

and is not symmetric and, therefore, its eigenvectors are not necessarily orthogonal. Thus as opposed to PCA, the CV's are often not perpendicular. As a consequence, covariance in the data causes the CVA model to fail, which is why spectral data must first undergo PCA. The last step in CVA is the transformation of the data on the basis of the retained CV's as

$$Z = XA^T \quad \text{Equation 15}$$

Hold-One-Out Cross Validation

HOO-CV is a method for estimating an algorithm's error rate (called the estimated error rate) for a population of spectra using data from which it was not trained. HOO-CV was used as part of this research to assess the estimated error rates of the mathematical modes created using PCA-CVA. HOO-CV is a useful method to estimate error rates when large data sets are not available for testing. (Effron & Tibshirani, 1993) HOO-CV computes the decision rules using all but one of the spectra in the data set. The HOO-CV estimated error rate is calculated by first determining whether the decision rule was correct on a held-out spectrum, \mathbf{x} , with true identity, \mathbf{y} , where $g^{\text{hold-out-x}}(\mathbf{x})$ denotes the identity of \mathbf{x} assigned by the "hold-one-out" decision rules. Error or misclassifications are assigned a 1 and correct classifications a 0, which is symbolically written as:

$$1 - \delta_{y,g(\mathbf{x})} \quad \text{Equation 16}$$

where the Kronecker delta denotes 1 if $y = g(x)$ and 0 otherwise.

$$\delta_{y,g(x)} = \begin{cases} 1 & \text{if } y = g(x) \\ 0 & \text{if } y \neq g(x) \end{cases} \quad \text{Equation 17}$$

The HOO-CV procedure is repeated for each spectrum in the data set and the results are averaged to calculate an estimated error rate shown in equation 18.

$$Err^{HOO-CV} = \frac{1}{n} \sum_{i=1}^n 1 - \delta_{y_i, g^{hold-out-x_i}(x_i)} \quad \text{Equation 18}$$

CHAPTER 6. SAMPLES AND SAMPLING MATRIX

Sample Procurement

Testing performed as part of this research was used to develop an analytical scheme to rapidly and reliably detect counterfeit drugs in the field. Attempts were made to procure “known” counterfeit drugs for testing. Many pharmaceutical companies that manufacture drugs known to be routinely counterfeited were contacted and requests for samples were made. However, no suppliers contacted were willing to provide test samples. For this reason, samples were ordered online from websites offering to sell prescription medication direct to a consumer located within the United States without a prescription. The drug ordered was sildenafil citrate 100-mg tablets. No prescription was provided at the time of any online purchase, so it was expected that the samples ordered online would be non-authentic versions of Pfizer’s VIAGRA 100-mg tablets. This is because prescription medications (like VIAGRA) are not allowed to be legally sold within the United States without a prescription. There are many reported reasons this drug is a target of counterfeiters in the United States and around the world, and reports with regard to the online purchase of VIAGRA indicate most are fake. (Fiore, 2012) For comparison, sixteen tablets expected to be authentic were purchased in the United States through FDA-governed pharmacies.

VIAGRA is not a drug commonly tested in crime labs in the United States. This is in spite of the fact that there are many reports of availability of non-authentic versions, and any non-authentic version of this drug sold in the United States is illegal. (35 U.S.C. § 271; Federal Food, Drug, and Cosmetic Act, 1938) The reason non-authentic VIAGRA samples are illegal is because they violate FDA regulations, and IP law. Reasons for this discrepancy are variable and include availability of resources within law enforcement, jurisdiction issues, and other

enforcement challenges. (Dean, 2013; Faucon & Whalen, 2012; Sen, 2012) However, it is a good drug of choice for inclusion in this testing for a few reasons. First, VIAGRA is currently under patent in the United States. (Ellis & Terret, 2002) Therefore, any non-authentic sample purchased in the United States, by definition, is either an illegal counterfeit or an illegal imitation version of the drug. Second, samples ordered online were purchased from “pharmacies” that appeared to be looking for repeat purchasers. At the time of purchase, each website requested contact emails for marketing purposes. They all also asked for permission to contact the purchaser to send a reminder when a “refill” was due. It was expected, therefore, that tablets received would likely contain at least some therapeutic amount of API. This was valuable from an analytical perspective because it required that methods used as part of this scheme be able to distinguish samples that were chemically similar to each other. It would be significantly easier to identify counterfeits or imitations if no API or a different API were present in the final dosage form.

Sample Summary

Websites from which tablets purchased online were ordered were found using various search terms and search engines. Purchases from any website were only made once, i.e., no repeat purchases were made from the same website by this researcher. Table 1 is a summary of all samples included in this testing from online purchases and purchases made from FDA-governed pharmacies in the United States.

Sample ID	Country of Postmarking on External Packaging
I1	India
I2	India
I3	India
I4	India
I5	India
S7	India
S8	China
SING1	Singapore (although blister packaging identifies country of manufacture as India)
SING2	Singapore (although blister packaging identifies country of manufacture as India)
S13	FDA-governed pharmacy in US
S14	FDA-governed pharmacy in US
S15	FDA-governed pharmacy in US
S16	FDA-governed pharmacy in US

Table 1. Summary of samples used for analytical testing.

Sampling Workflow

Analysis of each sample followed a step-by-step process that included photographic documentation, dimensional analysis, and physical/chemical characterization. The details of each method performed will be described in chapters 7 through 10, but the general testing process is summarized in figure 7.

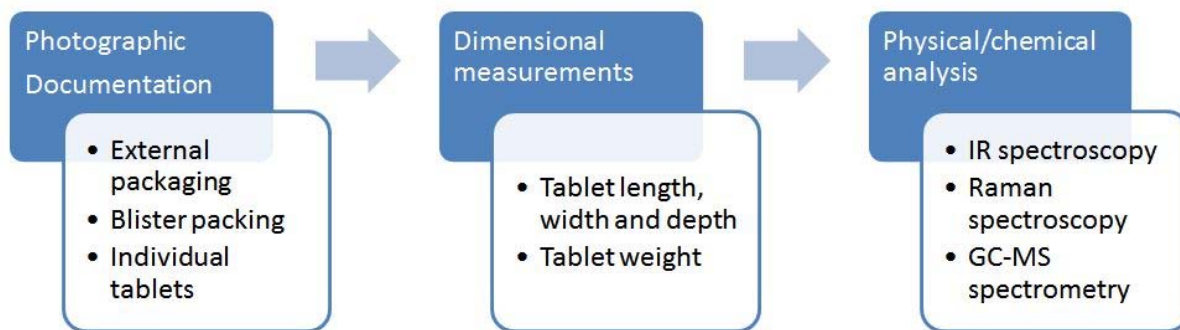


Figure 7. Analytical workflow for all test samples.

Sampling Matrix

Although attempts were made to analyze at least seven tablets from every sample, this was not always possible because in some cases seven tablets were not available for testing. Attempts were also made to analyze all seven tablets from each sample for GC-MS analysis. This was also not always possible because for some samples, a GC-MS system was not available at the time of analysis of that sample, or instrumental problems occurred that prevented analysis. Due to the fact that the entire tablet for GC-MS analysis was heated to generate a headspace appropriate for sampling, repeat testing at a different time was not an option if instrumental problems occurred.

Clarification of sampling is also necessary for replicate spectra collected from the same tablet. For some Raman spectra collected, there was a file corruption that occurred during data transport from the instrument. Although data for the sample was collected, in some cases, the third replicate analysis performed could not be included due to this file corruption.

To clarify the exact testing performed, a sample matrix showing all testing performed is shown in Tables 2 through 4.

Summary of All Measurements Performed	
tablet length measurements	210
tablet width measurements	210
tablet depth measurements	210
tablet weight measurements	210
infrared spectral measurements	231
Raman spectral measurements	177
GC-MS measurements	207
total number of measurements (not including photographs)	1455

Table 2. Summary of measurements performed on all samples.

sample ID	sample classification	Photographs	tablet length	tablet width	tablet depth	tablet weights
S13 T1	Authentic	Yes	3	3	3	3
S13 T2	Authentic	Yes	3	3	3	3
S13 T3	Authentic	Yes	3	3	3	3
S13 T4	Authentic	Yes	3	3	3	3
S14 T1	Authentic	Yes	3	3	3	3
S14 T2	Authentic	Yes	3	3	3	3
S14 T3	Authentic	Yes	3	3	3	3
S14 T4	Authentic	Yes	3	3	3	3
S15 T1	Authentic	Yes	3	3	3	3
S15 T2	Authentic	Yes	3	3	3	3
S15 T3	Authentic	Yes	3	3	3	3
S15 T4	Authentic	Yes	3	3	3	3
S16 T1	Authentic	Yes	3	3	3	3
S16 T2	Authentic	Yes	3	3	3	3
S16 T3	Authentic	Yes	3	3	3	3
S16 T4	Authentic	No	0	0	0	0
I1 T1	Illegal Imitation	Yes	3	3	3	3
I1 T2	Illegal Imitation	Yes	3	3	3	3
I1 T3	Illegal Imitation	Yes	3	3	3	3
I1 T4	Illegal Imitation	Yes	3	3	3	3
I1 T5	Illegal Imitation	Yes	3	3	3	3
I1 T6	Illegal Imitation	Yes	3	3	3	3
I1 T7	Illegal Imitation	Yes	3	3	3	3
I2 T1	Illegal Imitation	Yes	3	3	3	3
I2 T2	Illegal Imitation	Yes	3	3	3	3
I2 T3	Illegal Imitation	Yes	3	3	3	3
I2 T4	Illegal Imitation	Yes	3	3	3	3
I2 T5	Illegal Imitation	Yes	3	3	3	3
I2 T6	Illegal Imitation	Yes	3	3	3	3
I2 T7	Illegal Imitation	Yes	3	3	3	3
I3 T1	Illegal Imitation	Yes	3	3	3	3
I3 T2	Illegal Imitation	Yes	3	3	3	3
I3 T3	Illegal Imitation	Yes	3	3	3	3
I3 T4	Illegal Imitation	Yes	3	3	3	3
I3 T5	Illegal Imitation	Yes	3	3	3	3
I3 T6	Illegal Imitation	Yes	3	3	3	3
I3 T7	Illegal Imitation	Yes	3	3	3	3
I4 T1	Illegal Imitation	Yes	3	3	3	3
I4 T2	Illegal Imitation	Yes	3	3	3	3
I4 T3	Illegal Imitation	Yes	3	3	3	3
I4 T4	Illegal Imitation	Yes	3	3	3	3
I4 T5	Illegal Imitation	Yes	3	3	3	3
I4 T6	Illegal Imitation	Yes	3	3	3	3
I4 T7	Illegal Imitation	Yes	3	3	3	3
I5 T1	Illegal Imitation	Yes	3	3	3	3
I5 T2	Illegal Imitation	Yes	3	3	3	3
I5 T3	Illegal Imitation	Yes	3	3	3	3
I5 T4	Illegal Imitation	Yes	3	3	3	3
I5 T5	Illegal Imitation	Yes	3	3	3	3
I5 T6	Illegal Imitation	Yes	3	3	3	3
I5 T7	Illegal Imitation	Yes	3	3	3	3
S7 T1	Illegal Imitation	Yes	0	0	0	0
S7 T2	Illegal Imitation	Yes	3	3	3	3
S7 T3	Illegal Imitation	Yes	3	3	3	3
S7 T4	Illegal Imitation	Yes	0	0	0	0
S7 T5	Illegal Imitation	Yes	0	0	0	0
S7 T6	Illegal Imitation	Yes	0	0	0	0
S7 T7	Illegal Imitation	Yes	3	3	3	3
S7 T8	Illegal Imitation	Yes	0	0	0	0
S8 T1	Counterfeit	Yes	0	0	0	0
S8 T2	Counterfeit	Yes	0	0	0	0
S8 T3	Counterfeit	Yes	0	0	0	0
S8 T4	Counterfeit	Yes	3	3	3	3
S8 T5	Counterfeit	Yes	3	3	3	3
S8 T6	Counterfeit	Yes	0	0	0	0
S8 T7	Counterfeit	Yes	0	0	0	0
S8 T8	Counterfeit	Yes	3	3	3	3
SING1 T1	Illegal Imitation	Yes	3	3	3	3
SING1 T2	Illegal Imitation	Yes	3	3	3	3
SING1 T3	Illegal Imitation	Yes	3	3	3	3
SING1 T4	Illegal Imitation	Yes	3	3	3	3
SING1 T5	Illegal Imitation	Yes	3	3	3	3
SING1 T6	Illegal Imitation	Yes	3	3	3	3
SING1 T7	Illegal Imitation	Yes	3	3	3	3
SING2 T1	Illegal Imitation	Yes	3	3	3	3
SING2 T2	Illegal Imitation	Yes	3	3	3	3
SING2 T3	Illegal Imitation	Yes	3	3	3	3
SING2 T4	Illegal Imitation	Yes	3	3	3	3
SING2 T5	Illegal Imitation	Yes	3	3	3	3
SING2 T6	Illegal Imitation	Yes	3	3	3	3
SING2 T7	Illegal Imitation	Yes	3	3	3	3
Total Number of Measurements			210	210	210	210

Table 3. Summary of photography and dimensional measurements performed on each tablet.

sample ID	infrared spectra core	Raman spectra core	GC-MS at 60C standard fiber	GC-MS at 60C carboxen fiber	GC-MS at 110C standard fiber	GC-MS at 110C carboxen fiber
S13 T1	3	0	1	1	1	1
S13 T2	3	0	1	1	1	1
S13 T3	0	0	0	0	0	0
S13 T4	3	0	1	1	1	1
S14 T1	3	0	0	0	0	0
S14 T2	3	0	1	1	1	1
S14 T3	3	0	0	0	0	0
S14 T4	3	0	0	0	0	0
S15 T1	3	3	1	1	1	1
S15 T2	3	3	1	1	1	1
S15 T3	3	3	1	1	1	1
S15 T4	3	3	1	1	1	1
S16 T1	3	3	1	1	1	1
S16 T2	3	3	1	1	1	1
S16 T3	3	3	1	1	1	1
S16 T4	0	0	1	1	1	1
I1 T1	3	2	1	0	1	1
I1 T2	3	3	1	0	1	1
I1 T3	3	2	1	0	1	1
I1 T4	3	3	1	0	1	0
I1 T5	3	2	1	0	1	0
I1 T6	3	3	1	0	1	0
I1 T7	3	3	1	0	1	0
I2 T1	3	3	0	1	1	0
I2 T2	3	3	0	1	1	0
I2 T3	3	2	1	0	1	0
I2 T4	3	3	0	1	1	0
I2 T5	3	3	1	0	1	0
I2 T6	3	3	1	0	1	0
I2 T7	3	2	1	0	1	0
I3 T1	3	3	1	1	1	1
I3 T2	3	2	1	1	1	1
I3 T3	3	3	1	1	1	1
I3 T4	3	3	1	1	1	1
I3 T5	3	3	1	1	1	1
I3 T6	3	3	1	1	1	1
I3 T7	3	3	1	1	1	1
I4 T1	3	3	1	1	1	1
I4 T2	3	3	1	1	1	1
I4 T3	3	2	1	1	1	1
I4 T4	3	3	1	1	1	1
I4 T5	3	3	1	1	1	1
I4 T6	3	3	1	1	1	1
I4 T7	3	3	1	1	1	1
I5 T1	3	3	1	1	1	1
I5 T2	3	3	1	1	1	1
I5 T3	3	3	1	1	1	1
I5 T4	3	3	1	1	1	1
I5 T5	3	3	1	1	1	1
I5 T6	3	3	1	1	1	1
I5 T7	3	3	1	1	1	1
S7 T1	3	0	0	0	0	0
S7 T2	3	3	1	0	1	0
S7 T3	3	3	0	0	0	0
S7 T4	3	0	1	1	1	1
S7 T5	3	0	1	1	1	1
S7 T6	0	0	0	0	0	0
S7 T7	3	2	0	0	0	0
S7 T8	3	0	0	0	0	0
S8 T1	3	0	0	1	1	0
S8 T2	0	0	0	0	0	0
S8 T3	3	0	0	0	0	0
S8 T4	3	2	0	0	0	0
S8 T5	3	3	0	0	0	0
S8 T6	3	0	1	1	1	1
S8 T7	3	0	0	0	0	0
S8 T8	3	3	0	1	1	0
SING1 T1	3	3	0	0	0	0
SING1 T2	3	3	1	0	1	0
SING1 T3	3	3	1	0	1	0
SING1 T4	3	3	0	1	1	0
SING1 T5	3	3	0	0	0	0
SING1 T6	3	3	0	1	1	0
SING1 T7	3	3	0	0	0	0
SING2 T1	3	3	1	1	1	1
SING2 T2	3	3	1	1	1	1
SING2 T3	3	3	1	1	1	1
SING2 T4	3	3	1	1	1	1
SING2 T5	3	3	1	1	1	1
SING2 T6	3	3	1	1	1	1
SING2 T7	3	3	1	1	1	1
Total Number of Measurements	231	177	57	50	64	46

Table 4. Summary of infrared, Raman and GC-MS measurements performed on each tablet.

CHAPTER 7. DIMENSIONAL ANALYSIS AS A TOOL FOR IDENTIFICATION AND DIFFERENTIATION OF AUTHENTIC DRUGS

Introduction

The manufacture of pharmaceutical tablets is a complicated process. Raw materials are blended together using a variety of solvents, usually at elevated temperatures. These materials are ultimately dried and compressed into tablets of specified physical dimensions.

Manufacturing equipment such as the die's used to impress product-specific labeling into the tablet also change the physical features of the tablet. For coated tablets, coating materials and the process used to perform the coating may also impart upon the final dosage form characteristics that are specific to the manufacturer. Analysis and comparison of these dimensional measurements and other physical and chemical properties between authentic and non-authentic samples may sometimes result in the ability to quickly and easily differentiate authentic from non-authentic samples. (Jung, Ortiz, Limberger, & Mayorga, 2012) This data may be further used to classify counterfeit drugs providing investigative leads useful in establishing source or origin. They are also amongst the easiest of analyses to perform in the field.

Tablet weight is an important measurement because it is difficult, unless samples are manufactured identically using the same types and amounts of ingredients, to generate a reproducible tablet weight. An analytical balance will easily detect these differences, especially in cases where tablets might otherwise appear grossly to be the same. Physical dimensions such as length, width, depth, and overall tablet shape may also be different if different manufacturing equipment is used to press the final product. A caliper may be used to measure these properties. Tablet color and coating details will also depend upon both the raw materials used, as well as the process used to coat the tablet. Aside from color and chemical composition, coatings may

appear and behave differently. Photographs may be used to document these differences. In this study, photographs of tablets were taken and dimensional measurements were performed to determine whether or not it was possible to differentiate between authentic from non-authentic samples.

Experimental Details

Each tablet was weighed and photographed. The tablet's length, width, and depth were measured using a digital caliper. The average weight, length, width, and depth were calculated for all tablets of a given sample. Results were compared for different tablets of the same sample, as well as for different samples.

Photography

Photographs were taken using a Samsung Galaxy phone with camera, model SCH-1535, Android version 4.1.2. Tablet images were collected from both sides of each tablet at three different distances. Images captured from a distance of 60.4 mm were selected for inclusion in this summary. Magnification was set to 4.0 times, but autofocus was used.

Tablet Dimensions

Measurements of tablet length, width, and depth were taken for each tablet using a Ference Construction Co. digital caliper. For each dimension, three measurements were taken for each tablet. The "AVERAGE" function of Microsoft Excel was used to calculate the tablet's dimension value from the three measured values (Microsoft Excel 2010 running on Windows 7 Enterprise, Service Pack 1, 64-bit Operating System). The average dimension and standard deviation for each sample was then calculated from the determined values for each tablet of the sample using the "AVERAGE" and "STDEV" functions within Microsoft Excel. From these

values, the %RSD was calculated for each sample using Microsoft Excel with the formula “=(STDEV/AVERAGE)*100”.

Tablet Weights

Tablet weights were measured using two different balances. The balance used was based upon availability at the time of analysis. Each balance had a readability as low as 0.1 mg. Both balances were under service contracts for calibration at all times measurements were made. For each tablet, sample weight was measured three times. The balance was tared between measurements. The “AVERAGE” function of Microsoft Excel was applied to the three values to determine tablet weight (Microsoft Excel 2010 running on Windows 7 Enterprise, Service Pak 1, 64-bit Operating System). The average weight and standard deviation of the sample were then calculated from the weights all tablets of the sample using the “AVERAGE” and “STDEV” functions within Microsoft Excel. The %RSD was using Microsoft Excel with the formula “=(STDEV/AVERAGE)*100”.

Results and Discussion

It was possible to differentiate the authentic samples from all non-authentic samples based upon visual observation. For eight of the nine non-authentic samples, the tablets could very easily be distinguished from the authentic samples with the unaided eye. These eight non-authentic samples exhibited obvious differences in color, tool-mark impressions, and even shape, from the authentic samples. Weight measurements were also frequently different from each other. The ninth sample, sample S8, was counterfeit and was more similar in general appearance than the other eight samples to the authentic samples. These tablets were still differentiable, however, by visual observation, when compared with authentic VIAGRA. Just like for authentic 100-mg VIAGRA tablets, the tablets of sample S8 were coated, light-blue tablets. They were

labeled “Pfizer” on one side and “VGR 100” on the reverse side. Figure 8 shows the front of a tablet from sample S8 alongside a tablet of an authentic sample. Figure 9 shows the back side of both tablets. Although the counterfeit sample is intended to look like an authentic VIAGRA, the appearance of this tablet is different from that of authentic VIAGRA when a side-by-side comparison of the two samples is made. Aside from size and color, tool-mark impressions appeared different between tablets of the authentic samples and the tablets of sample S8. The benefit of having an authentic sample for comparison made this differentiation based upon visual observation alone quite easy. If no authentic for comparison was available, it would have been more difficult to identify this tablet as a counterfeit without measuring tablet size and/or weight.

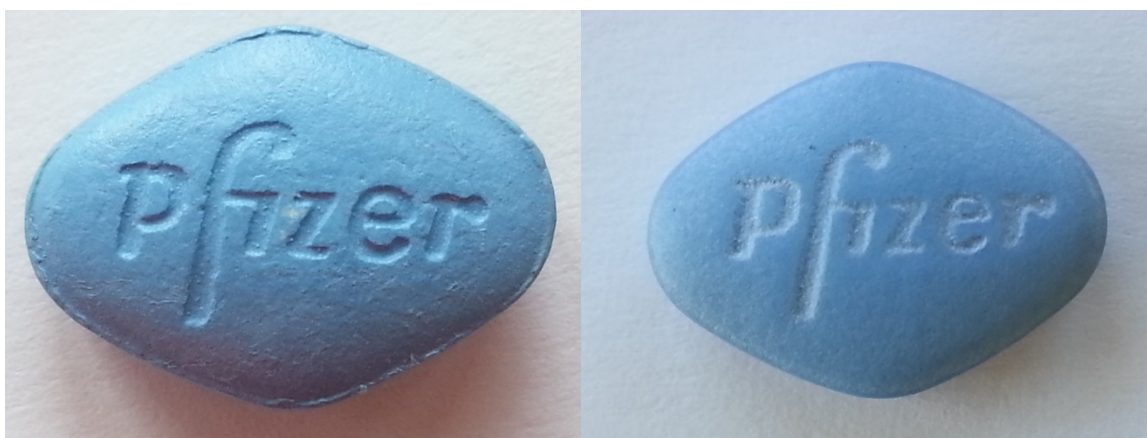


Figure 8. Front side of a counterfeit VIAGRA tablet (left) alongside an authentic VIAGRA tablet (right). Both tablets are displayed on the same scale.



Figure 9. Back side of a counterfeit VIAGRA tablet (left) alongside an authentic VIAGRA tablet (right). Both tablets are displayed on the same scale.

Table 5 summarizes the dimensional analysis for all the samples analyzed. The tablets of sample S8 are slightly larger than the authentic samples in length and width, and weighed approximately 100 mg more than did the authentic samples. Standard deviations were also calculated for each measurement of each tablet and are shown in this table. The relative standard deviation (RSD) amongst different tablets of the same samples was always less than 2% for each sample. This shows that for a specific sample, all measured values were consistent from tablet to tablet.

Sample Number	Length (mm)	St Dev	%RSD	Width (mm)	St Dev	%RSD	Depth (mm)	St Dev	%RSD	Weight (mg)	St Dev	%RSD
I1	14.39	0.01521	0.11	10.42	0.01894	0.18	5.57	0.0969	1.74	609.1	7.01	1.15
I2	14.63	0.02085	0.14	10.48	0.01755	0.17	5.36	0.0398	0.74	557.9	5.37	0.96
I3	11.62	0.01357	0.12	11.85	0.02460	0.21	5.35	0.0581	1.09	528.1	4.63	0.88
I4	14.43	0.02175	0.15	10.46	0.00970	0.09	5.66	0.0251	0.44	602.4	7.67	1.27
I5	14.52	0.01538	0.11	10.50	0.00720	0.07	5.10	0.0316	0.62	642.3	4.64	0.72
S13 (authentic)	14.77	0.02722	0.18	10.65	0.07120	0.67	5.77	0.0160	0.28	633.0	10.59	1.67
S14 (authentic)	14.70	0.04787	0.33	10.57	0.02722	0.26	5.79	0.0397	0.69	633.8	9.36	1.48
S15 (authentic)	14.75	0.02331	0.16	10.62	0.00694	0.07	5.77	0.00739	0.13	618.7	12.08	1.95
S16 (authentic)	14.71	0.01644	0.11	10.61	0.01262	0.12	5.78	0.00839	0.15	615.7	5.36	0.87
S7	14.77	0.00839	0.06	10.54	0.01836	0.17	4.82	0.0735	1.52	502.3	7.31	1.45
S8	14.92	0.00839	0.06	10.78	0.01333	0.12	5.68	0.0301	0.53	733.6	5.15	0.70
SING1	11.69	0.01638	0.14	11.92	0.01835	0.15	5.47	0.0507	0.93	541.1	4.49	0.83
SING2	11.72	0.02193	0.19	11.95	0.03173	0.27	5.46	0.0305	0.56	533.2	5.97	1.12

Table 5. Summary of dimensional measurements of samples analyzed.

Although it was possible to distinguish the non-authentic samples from the authentic samples, analysis of variance (ANOVA) was applied to the data to determine whether the variance could be used to differentiate non-authentic samples that were very similar in appearance to each other. For example, samples I1 and I4 were very similar in dimensional measurements and physical appearance to each other. Using the physical measurements of length, width, depth, and weight, t-tests indicate that there is a statistically significant difference between I1 and I4 at the 5% level of significance. However, using the physical measurements of length, width, depth, and weight, ANOVA analysis of the four authentic samples indicates there is also a statistically significant difference even amongst these authentic samples. This variance in these four authentic samples indicates t-tests and ANOVA analysis of the physical-measurements data collected from these samples alone is not an appropriate method of discrimination.

The box plots generated from ANOVA analysis of the length measurements of authentic samples is shown in figure 10. The box plots generated from the t-test analysis of the length measurements of I1 and I4 are shown in figure 11. The box plots highlight the median value for each sample. Although only the results from the length measurements are shown, the same general amount of variance was observed for the measurements of width, depth, and weight.

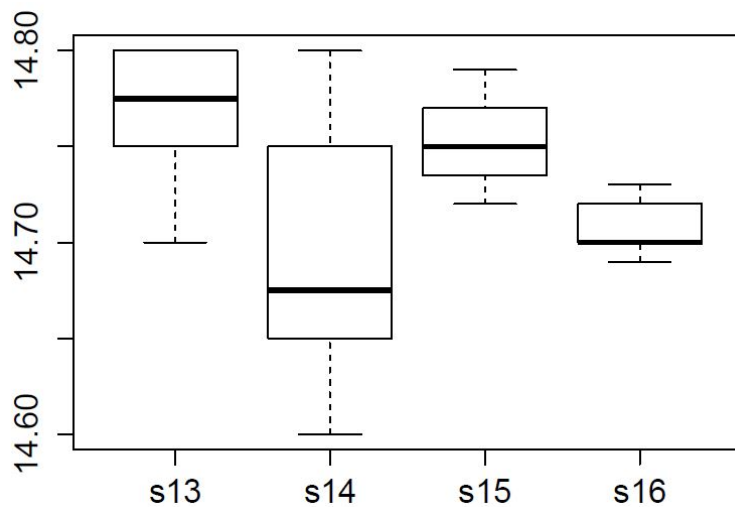


Figure 10. Box plots generated from length measurements of the authentic samples.

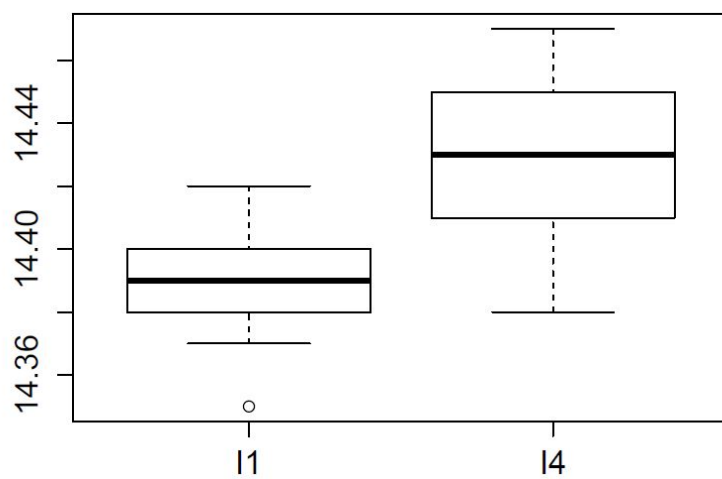


Figure 11. Box plots generated from length measurements of samples I1 and I4.

Figures 12 through 19 show the front and back sides of tablets of each of the other eight non-authentic samples.



Figure 12. Images of the front and back of a tablet of I1.



Figure 13. Images of the front and back of a tablet of I2.



Figure 14. Images of the front and back of a tablet of I3.



Figure 15. Images of the front and back of a tablet from I4.



Figure 16. Images of the front and back of a tablet from I5.

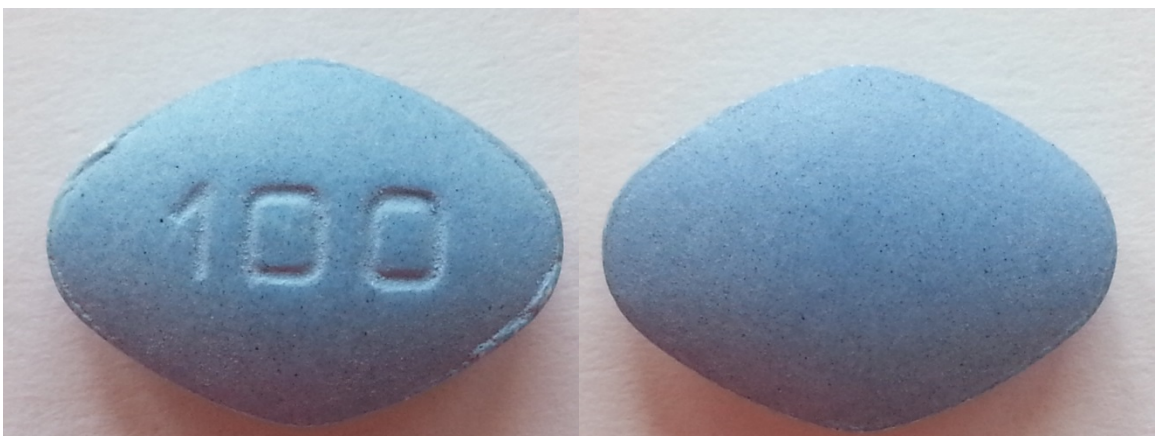


Figure 17. Images of the front and back of a tablet from S7.



Figure 18. Images of the front and back of a tablet from SING1.



Figure 19. Images of the front and back of a tablet from SING2.

Summary and Conclusion

This research shows that detection and identification of all of the non-authentic samples was possible based upon visual observation. In addition, tablet weights and other dimensional measurements could be used to differentiate the non-authentic samples from the authentic versions. These measurements were consistent for different tablets of the same sample. For all tablets within a sample, the percent RSD for all measurements of length, width, depth, and weight were less than 0.34, 0.68, 1.75 and 1.96, respectively. T-tests and ANOVA analysis of the physical-measurements data collected from these samples alone is not an appropriate method

of discrimination. The within-group variance of these measurements is equal to or greater than the between-group variance.

CHAPTER 8. INVESTIGATION AND EVALUATION OF CHEMICAL AND PHYSICAL PROPERTIES OF FINAL DOSAGE FORMS USING INFRARED SPECTROSCOPY

Introduction

Pharmaceutical tablets are typically comprised of active and inactive ingredients blended together using specific manufacturing processes. Specific manufacturing processes are used because different processes may alter these ingredients, causing changes in both physical and chemical form. An example of a change in physical form may be the conversion from one solid-state form of the drug to another; an example of a change in chemical form may be the formation of degradation products. Both the active (and inactive) ingredients may undergo changes in solid-state form. An example of this type of transition is the conversion of a drug substance from a crystalline form to an amorphous form.

Drugs may also sorb water or solvent to form hydrates or solvates. Some water is sorbed interstitially. This water does not become part of the crystal structure of the drug or incorporate itself in the drug chemically. Water may also be sorbed resulting in differences in crystal structure between two hydrated forms of a drug. In these crystalline hydrates, water is part of the drug's crystal lattice. These hydrates and solvates may or may not desorb during the final manufacturing steps.

Ingredients may also physically or chemically react with each other during tablet manufacture or storage. An example of a physical interaction is the formation of a eutectic. An example of a chemical interaction would be the formation of a degradation product. These interactions may result in tablets that exhibit differences in therapeutic effects, storage stability, and physical or chemical composition.

When manufacturing processes are well controlled and adhere to regulatory guidelines as is typical for an authentic product sold in the United States, the physical and chemical properties of the final dosage form is well controlled and reproducible. The ability to detect and identify the physical and chemical form of the final dosage form in a reliable manner is useful, providing a compositional fingerprint that is representative of the authentic product and may be used to differentiate authentic from non-authentic tablets. This fingerprint may also be used to classify counterfeit drugs, providing investigative leads useful in establishing source or origin.

Infrared spectroscopy is used to evaluate the chemical and physical form of tablets and other drug products. Data can be evaluated many different ways when applied to the analytical challenges associated with counterfeit drugs. In this study, infrared spectra were compared to differentiate authentic from non-authentic samples. The reproducibility of spectra collected from different tablets of a sample was also evaluated. Spectra were then evaluated to establish differences in the relative concentration of the API. Finally, chemometrics analysis, specifically PCA-CVA with HOO-CV, was performed to classify samples and determine an estimated error rate for this classification. Spectra used in this comparison were collected from the core matrix of the tablet.

Experimental Details

Instrumentation

Infrared spectra were collected using a HazMatID™ Elite infrared spectrometer (Smiths Detection, Danbury, CT). Performance of the spectrometer was tested at the start and end of every work day. The system always passed performance-test criteria. The performance test method used was the method recommended by the instrument manufacturer. This test requires

that the performance standard meets a minimum library match factor when compared with a reference standard spectrum.

The HazMatID Elite is specifically intended for field use. Some of the specifications for this system, especially those intended to support portability and ruggedization of the instrument, are shown in Table 6. An image of the system is shown in figure 20.

HazMatID Elite Specifications for Portability and Ruggedization	
Compact size	10 5/8 in x 5 5/8 in x 3 1/8 in)
Weight	2.29 kg
Operating Environmental Temperature	-20°C to 50°C
Operating Environmental Humidity	0-100%
Decontamination	IP-67 rated and sealed for decontamination by immersion
User interface	4.3 inches internally bonded LCD color display for high visibility in direct sunlight conditions; individually lit keypad and instructional graphics guide users through the operation of the device
Power	Rechargeable lithium-ion battery for 4 hours of operation; compatible with disposable 123A battery
Repeater	RF repeater for extending the wireless data transfer range
Colors	Olive drab or yellow
Wireless	Embedded RF modem for 1 km line-of-sight data transfer and command control; FIPS 140-2 compliant encryption; GPS included

Table 6. HazMatID Elite specifications for portability and ruggedization of importance to this study.



Figure 20. Photograph of HazMatID Elite diamond ATR FT-IR spectrometer. Courtesy of Smiths Detection, Danbury, CT.

Infrared Method

Prior to each sample analysis, the diamond IRE was cleaned using a low-lint tissue and, if necessary, with an appropriate solvent. A background spectrum was collected using the default method for the instrument set for 8-cm^{-1} resolution and 32 co-added scans. Each tablet was gently crushed and a small amount of the tablet's core was pressed against the diamond area until the instrument screen displayed in green. In order for this green readout to appear, the absorbance signal level for the spectrum's largest absorption band must reach a value of at least 0.11. A sample spectrum was then collected. The infrared spectrum was automatically calculated and displayed on the screen of the instrument. For each tablet, three infrared spectra from different samples of each tablet's core were collected.

Data Analysis and Chemometrics

All spectra were then exported from the HazMatID Elite via a USB storage hub and transferred to a personal computer. Each spectrum was opened using the Grams Suite 9.0 software (Thermo Fisher Scientific, Philadelphia, PA). Using Grams, a linear multipoint baseline correction was performed and corrected to account for diamond uncompensation in the spectral region between 2350 cm^{-1} and 1850 cm^{-1} . Using the Grams Add-On Excel Exchange function, spectra were exported to Microsoft Excel (Microsoft Excel 2010 running on Windows 7 Enterprise, Service Pak 1, 64-bit Operating System). Within Microsoft Excel, each spectrum was normalized to an area under the curve equal to one. The normalized spectrum was then imported to Grams using the Grams Add-On Excel Exchange.

The chemometric methods of PCA and CVA were applied to investigate the classification and discrimination power of infrared spectroscopy. Prior to chemometric analysis, the spectral region between 2350 cm^{-1} and 1850 cm^{-1} was deleted from all spectra. Non-authentic samples were sorted into seven groups based upon physical appearance, dimensions, and receipt date; authentic samples were categorized into a single group. The deconvolution data, specifically the peak positions and areas, also were analyzed using HOO-CV PCA-CVA to determine an estimated error rate for the classification of sildenafil citrate tablets.

Results and Discussion

It was possible to differentiate the authentic samples from all non-authentic samples using this method. In most cases, differences in spectra were small but reproducible. Using PCA-CVA, 3D-scores plots were created and visual separation of samples was observed. This observation indicates that not only can infrared spectroscopy be used to differentiate authentic from non-authentic samples, but also that this method may be used to sort non-authentic samples

and ultimately lead to the establishment of provenance. Using HOO-CV, an estimated error rate of 2.16% was calculated using 12 principal component's (PC's). The error was due to the misclassification of samples I1 and I4. A review of the infrared spectra shows that this misclassification is likely due to differing amounts of water in the samples. Otherwise, the spectra were indistinguishable. It is likely based on all other data collected that these two lots share a common origin.

Figures 21 through 29 show the average infrared spectrum of an authentic sample compared with the average spectrum from each of the nine non-authentic samples. Note that with the exception of sample S8, differences in the fingerprint region of the spectra of the non-authentic samples were small indicating that the chemical composition of the non-authentic samples was similar, but not identical to, the chemical composition of the authentic samples. Therefore, it was possible to differentiate all non-authentic samples from the authentic ones. Sample S8 contained an additional broad absorption band of high intensity that is likely due to the presence of calcium sulfate in the sample.

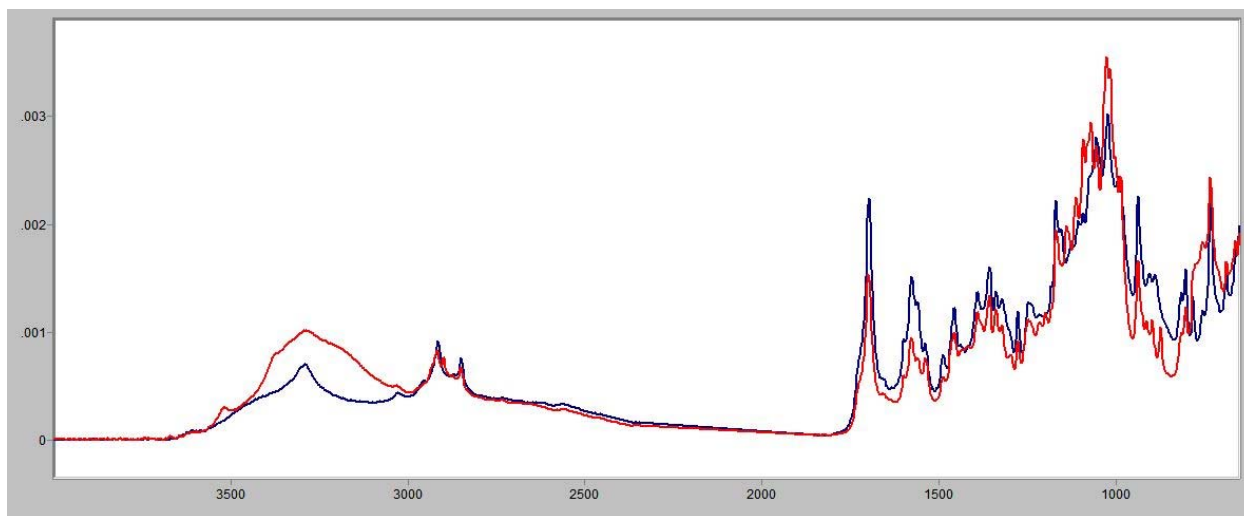


Figure 21. Infrared spectrum of authentic sample shown in blue compared with non-authentic I1 shown in red (spectra are area normalized).

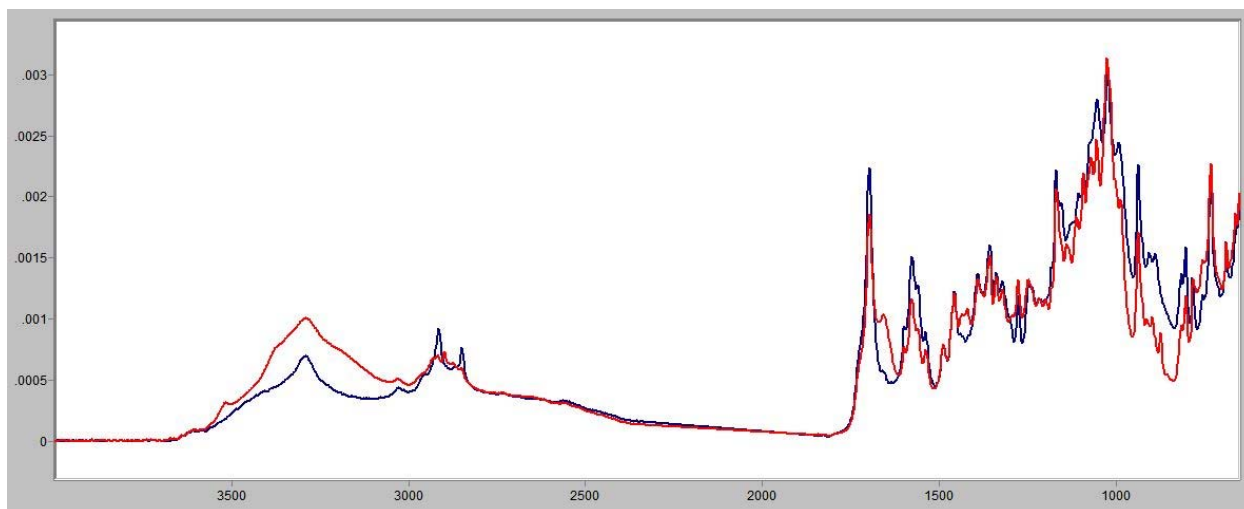


Figure 22. Infrared spectrum of authentic sample shown in blue compared with non-authentic I2 shown in red (spectra are area normalized).

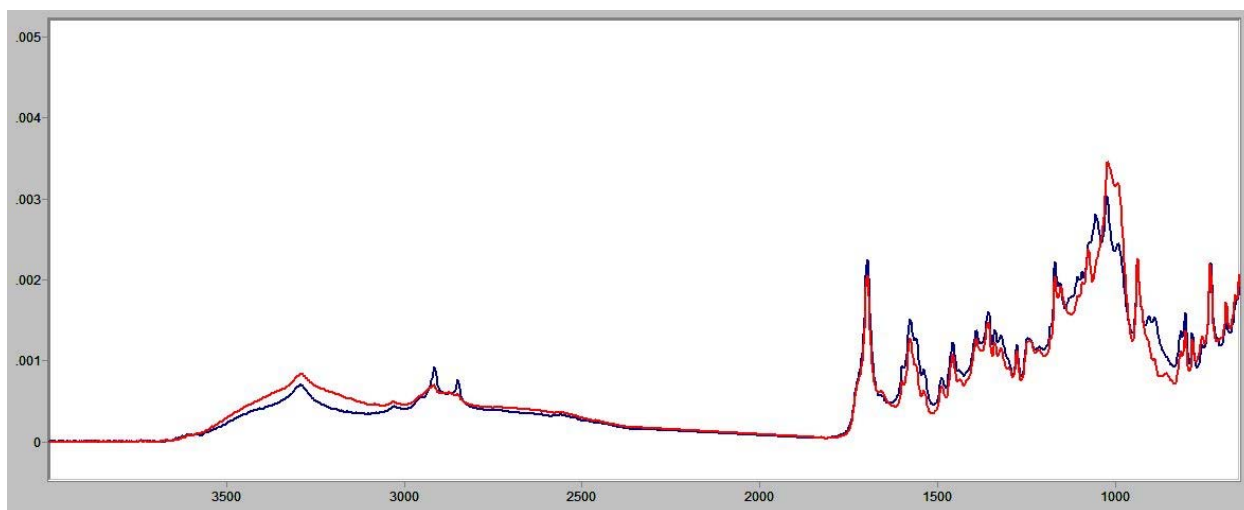


Figure 23. Infrared spectrum of authentic sample shown in blue compared with non-authentic I3 shown in red (spectra are area normalized).

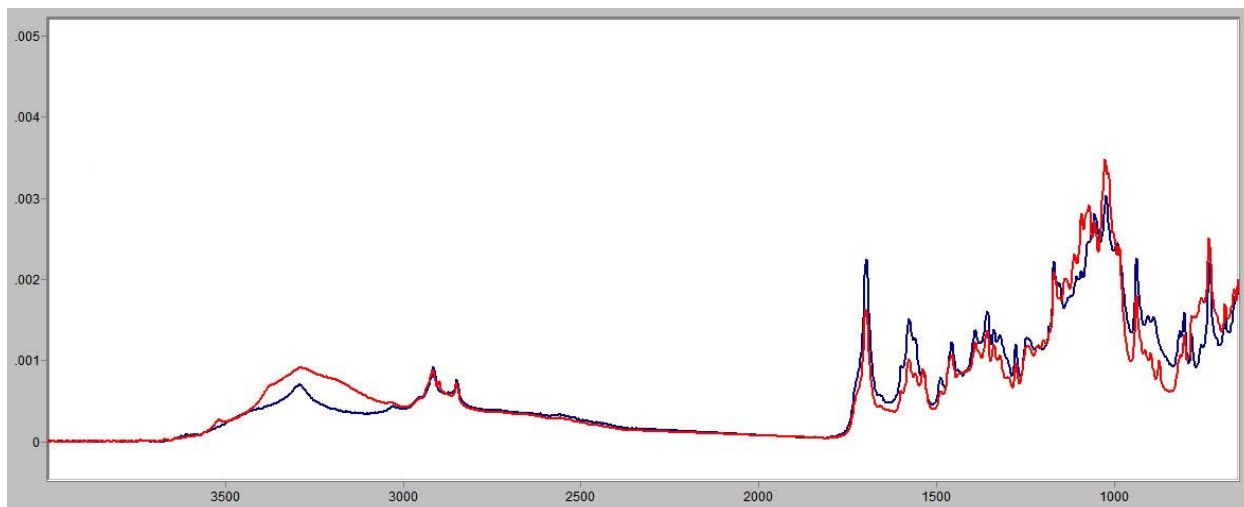


Figure 24. Infrared spectrum of authentic sample shown in blue compared with non-authentic I4 shown in red (spectra are area normalized).

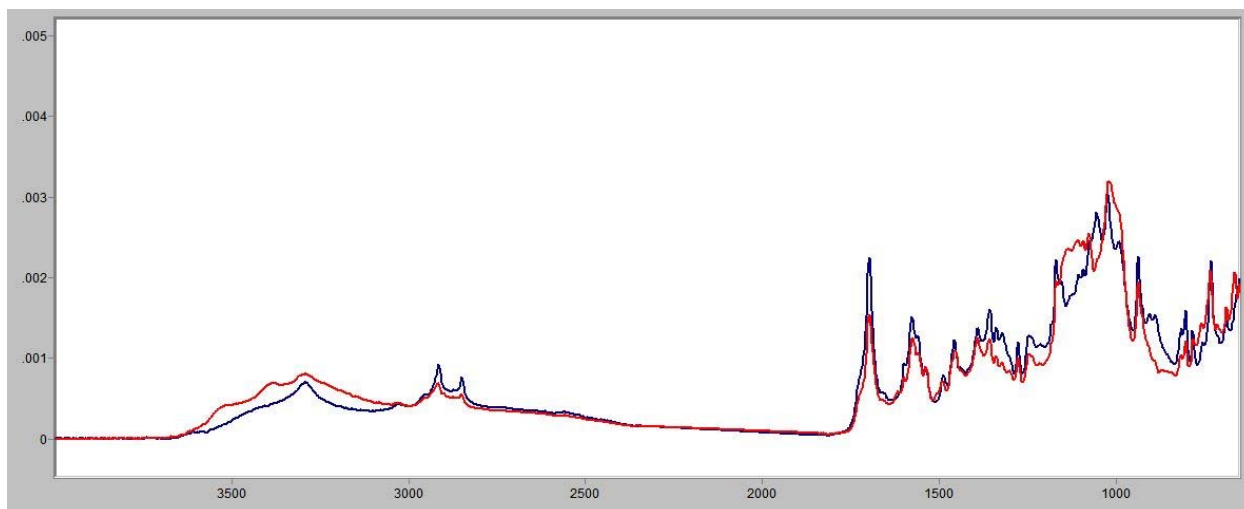


Figure 25. Infrared spectrum of authentic sample shown in blue compared with non-authentic I5 shown in red (spectra are area normalized).

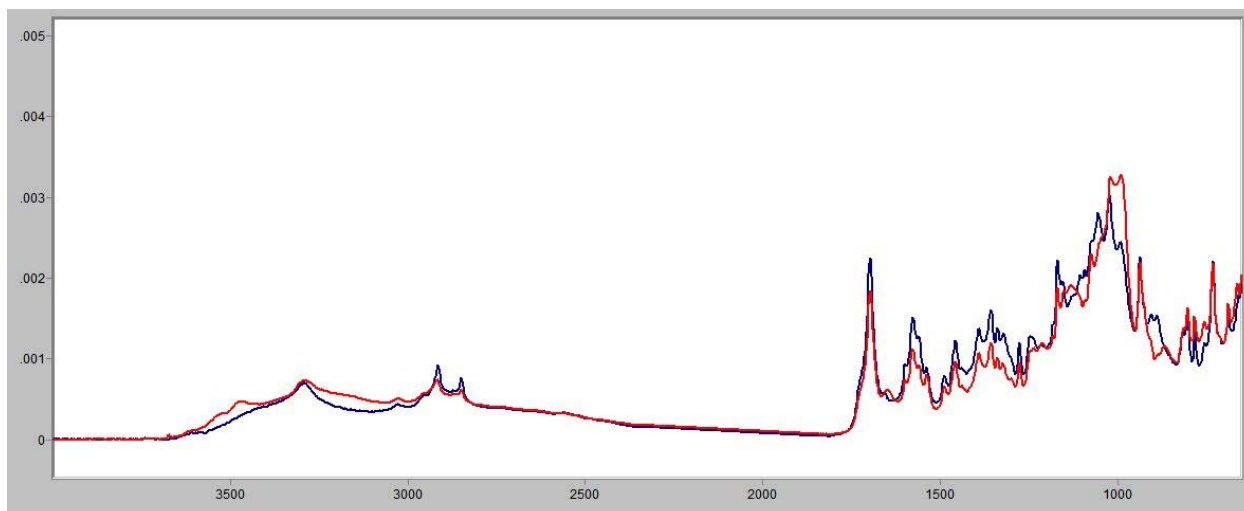


Figure 26. Infrared spectrum of authentic sample compared shown in blue with non-authentic S7 shown in red (spectra are area normalized).

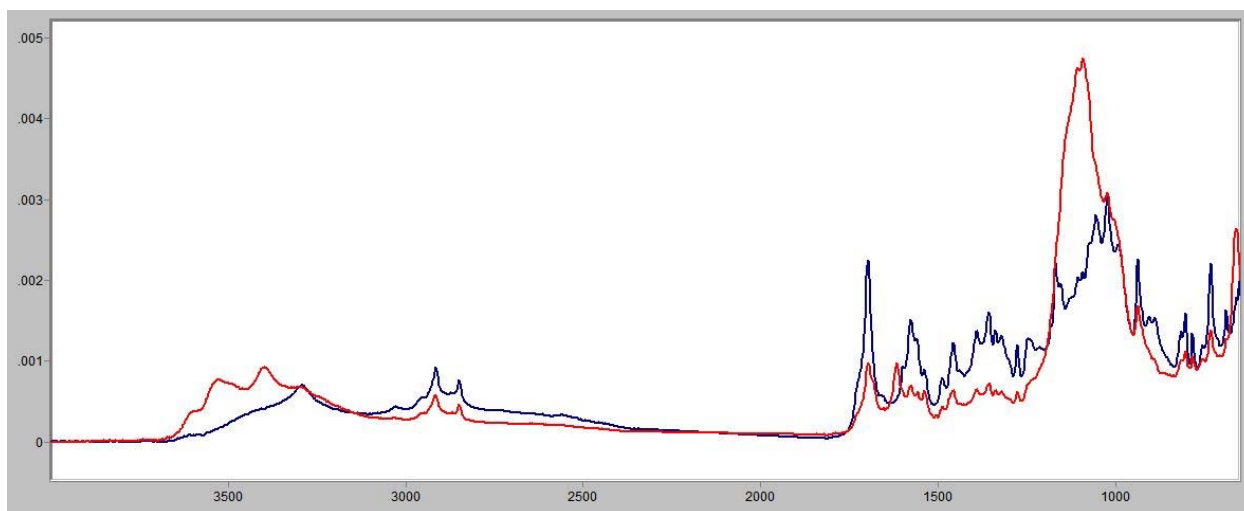


Figure 27. Infrared spectrum of authentic sample shown in blue compared with non-authentic S8 shown in red (spectra are area normalized).

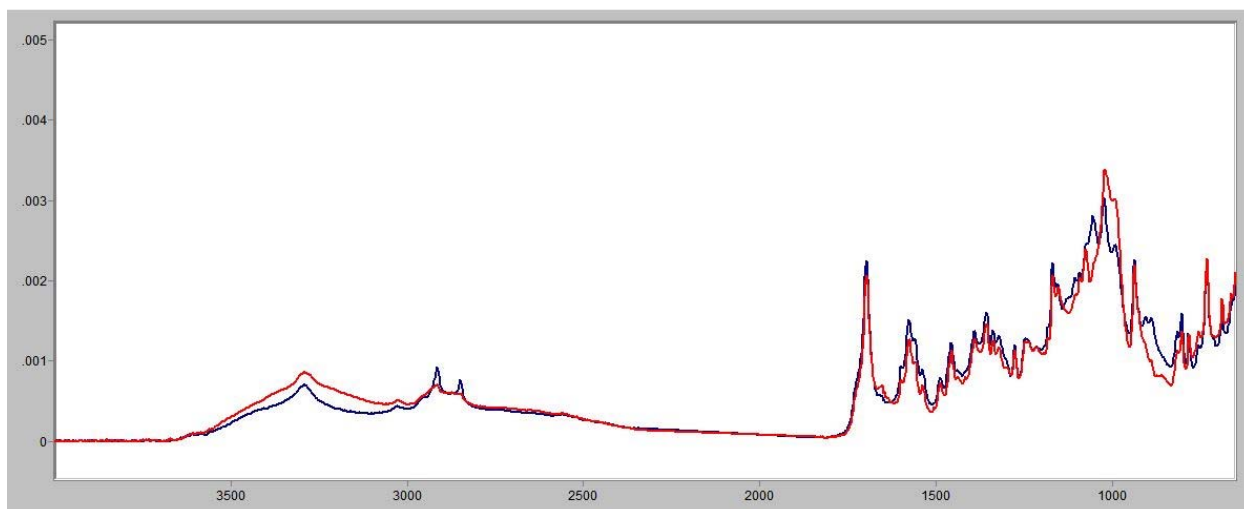


Figure 28. Infrared spectrum of authentic sample shown in blue compared with non-authentic SING1 shown in red (spectra are area normalized).

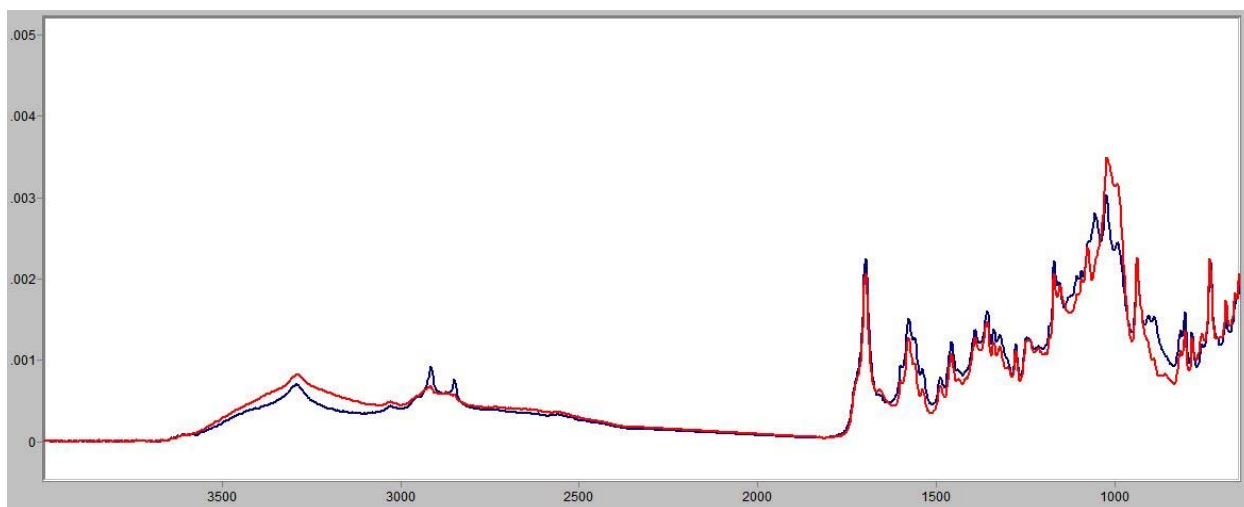


Figure 29. Infrared spectrum of authentic sample shown in blue compared with non-authentic SING2 shown in red (spectra are area normalized).

Although only the average spectrum for each sample is shown in the preceding nine figures, all of the spectra collected from each tablet and from the same sample were consistent with each other. There was some very small variance in the intensities of absorption bands within a sample, but there wasn't a single instance where two spectra from the same sample

revealed different absorption bands by visual inspection performed by this researcher. Figure 30 shows the 21 spectra collected from the tablet core of the tablets of sample I3. The variance from spectrum to spectrum shown in these figure were typical of the variance observed in spectra collected from all tablets of a single sample.

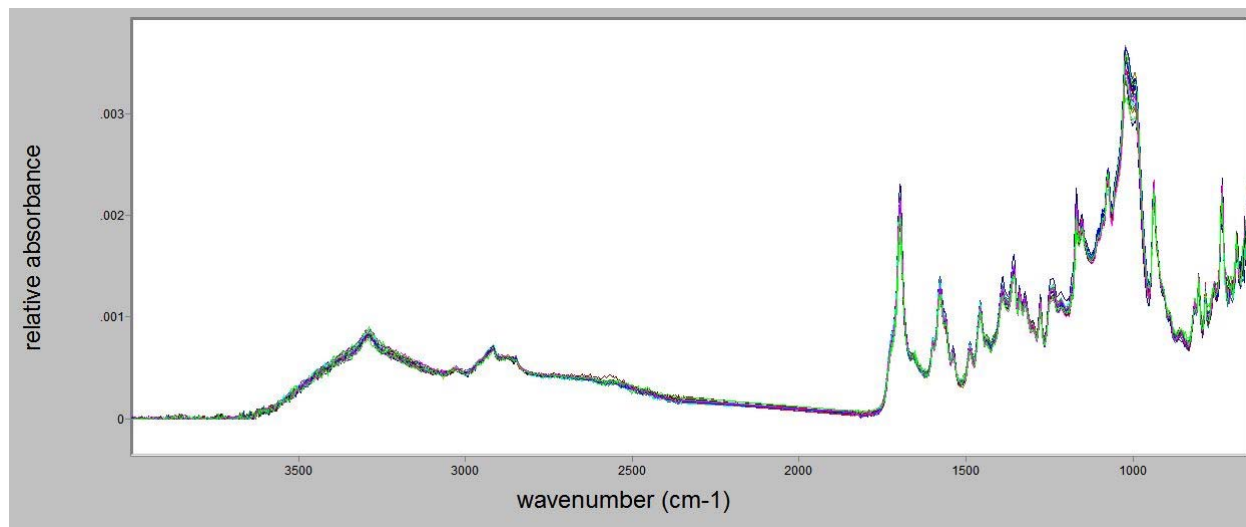


Figure 30. Twenty-one spectra collected from seven tablets of sample I3 (spectra are area normalized).

Figures 31 and 32 show the standard deviation of the absorbance values of each sample plotted as a function of wavenumber. Figure 31 shows the data in the fingerprint region of the spectrum and Figure 32 shows the data in the hydrogen-bonding region of the spectrum. The standard deviation of the absorbance is variable across the spectrum. Different samples are more variable than others in different regions of the spectrum. This indicates that variance is directly related to the physical and chemical compositions of the sample, i.e., absorption bands in some samples are more variable than they are in others. This data also indicates that the amount of variance is not necessarily indicative of whether or not a sample is authentic. Although authentic sample (S13) shows some of the least variance across the spectrum, it has the greatest amount of variance of all samples at 2915 cm^{-1} and 2850 cm^{-1} . This observation is consistent with the

hypothesis that this sample, although manufactured in a well-controlled manner, has sorbed water which causes variance in these two absorption bands.

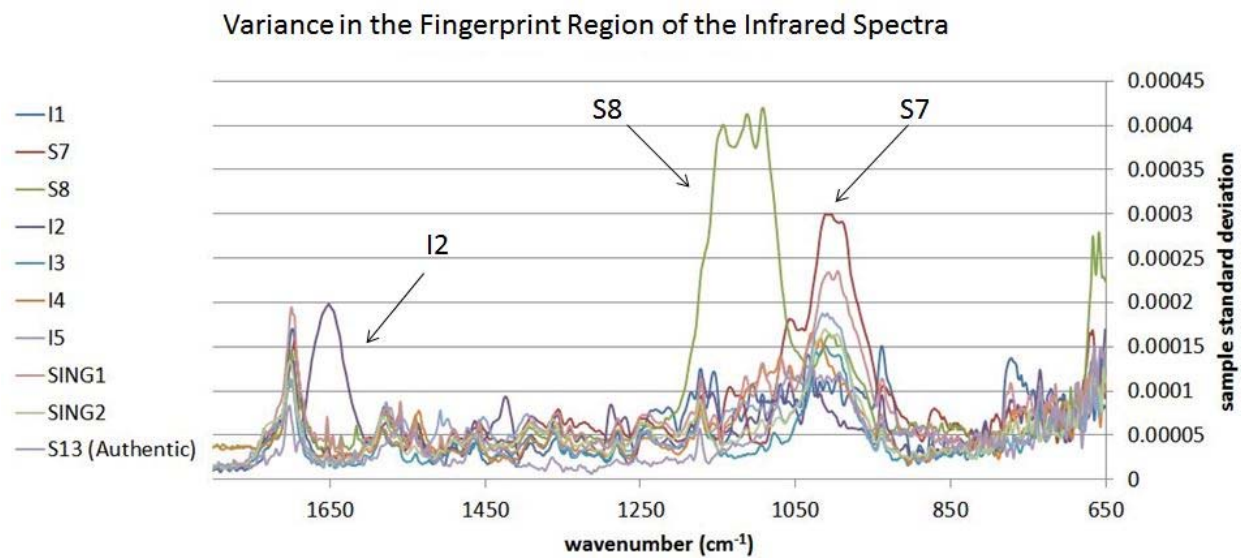


Figure 31. Variance expressed as the standard deviation at each wavenumber in the fingerprint region of the spectrum.

Variance in the Hydrogen-Bonding Region of the Infrared Spectra

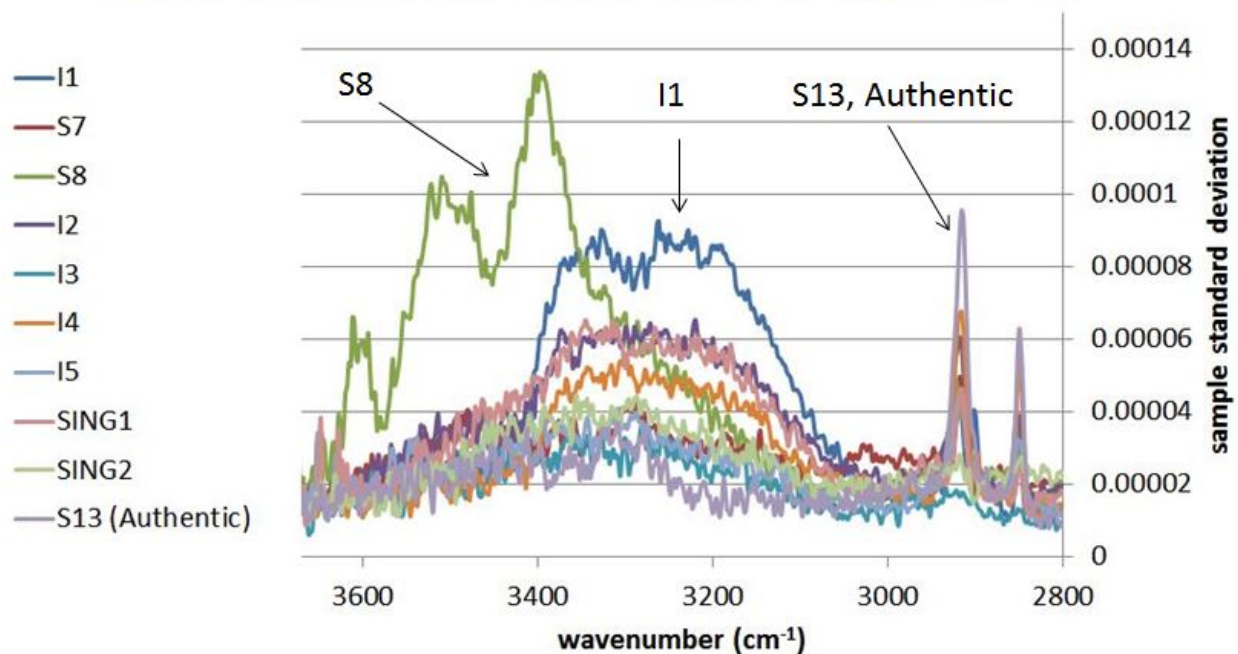


Figure 32. Variance expressed as the standard deviation at each wavenumber in the hydrogen-bonding region of the spectrum.

Sample I2 showed the greatest amount of variance of all samples at 1655 cm⁻¹. Figure 33 shows an overlay of all of the spectra collected from sample I2. Note that in this sample, the greatest amount of variance is evident in the absorption band at 1655 cm⁻¹. Figure 34 the same overlay expanded to see the absorption band at 1655 cm⁻¹ more clearly. In this instance, the cause of this spectral variance is unknown. Although the variance in the authentic samples can be explained by the presence of different amounts of water, interpretation of variance in the infrared spectra in this and some of the other samples was not as straightforward.

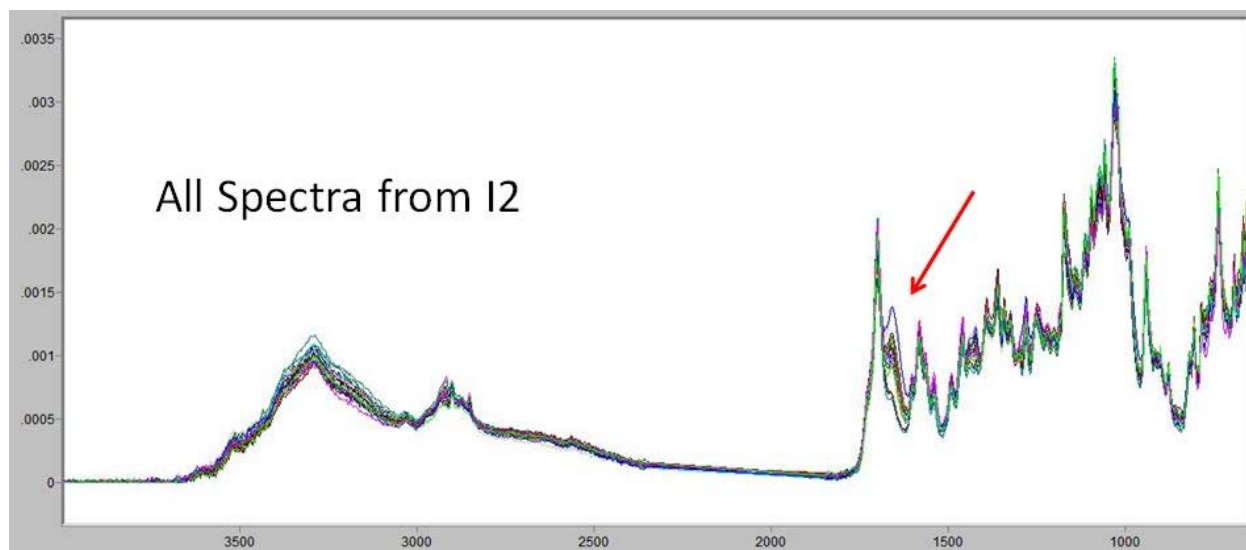


Figure 33. All infrared spectra collected from non-authentic sample I2 (spectra are area normalized).

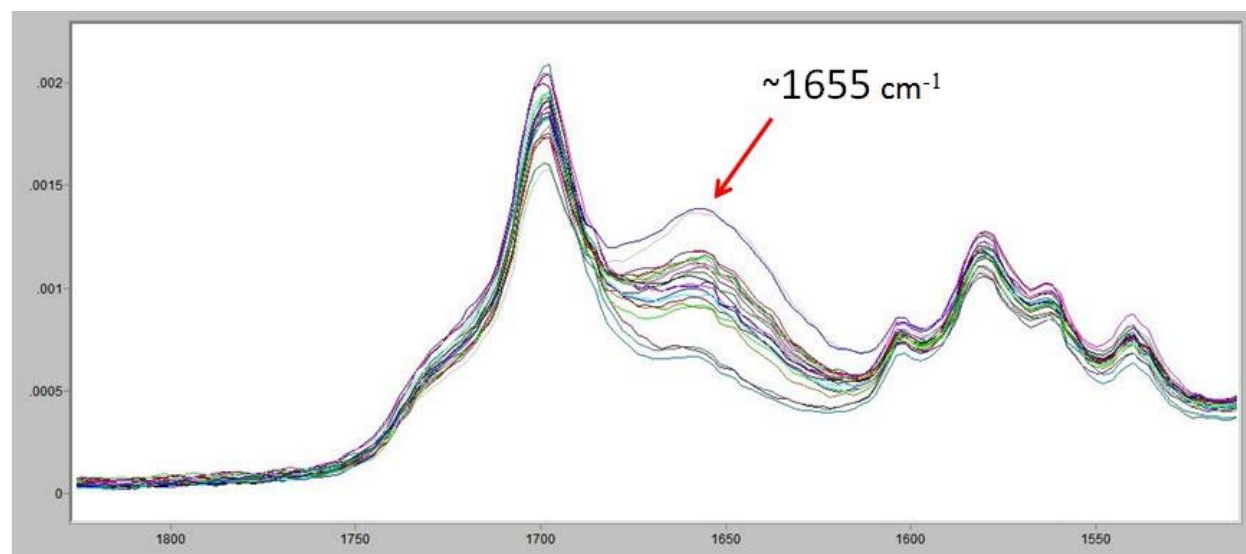


Figure 34. All infrared spectra collected from non-authentic sample I2 at 1655 cm^{-1} (spectra are area normalized)

From this infrared data, it was also possible to show that eight of the nine non-authentic samples contained less than 100 mg of sildenafil citrate, in spite of the fact that all were purported to contain 100 mg of this API. This type of analysis using infrared spectroscopy was possible for these samples because tablet weights for these eight samples were measured and

were lower than or approximately equal to what they were for the authentic VIAGRA. Therefore, the percent by weight of sildenafil citrate in these samples should be equal to or higher than for the authentic VIAGRA. Since the spectra are area normalized and the infrared spectra were very similar, absorption bands due only to sildenafil citrate could be reviewed to look for relative concentrations of sildenafil citrate. In all eight of these samples, the absorption band due to sildenafil citrate at 1697 cm^{-1} was lower in intensity than it was for the authentic VIAGRA. Therefore, the non-authentic samples could not contain 100 mg of sildenafil citrate (as purported). This band intensity should be the same or higher than it is for these tablets if they did, in fact, contain 100 mg of sildenafil citrate. It was not possible to determine whether or not the ninth non-authentic sample contained less than 100 mg of sildenafil citrate because the tablet weight for this sample was significantly higher than for authentic samples and, therefore, the absorption band intensity for area normalized spectra should be lower. In addition, the infrared spectrum for this sample was quite different than it was for the authentic sample. This is also a problem when performing this type of analysis because intensities become distorted during normalization due to differences in absorption-band intensities due to the presence of different chemical functional groups. Aside from this relative evaluation, no attempts were made to determine quantitatively the amount of sildenafil citrate present in these samples using infrared spectroscopy or any other technology.

Figure 35 shows an overlay of the spectrum at this absorbance at 1697 cm^{-1} for the authentic and non-authentic samples. The spectrum of the authentic sample is shown in red and all other spectra shown are of the non-authentic samples (except S8). For all samples except for sample S8, this indicates that less than the purported amount of 100 mg of sildenafil citrate is present in the sample.

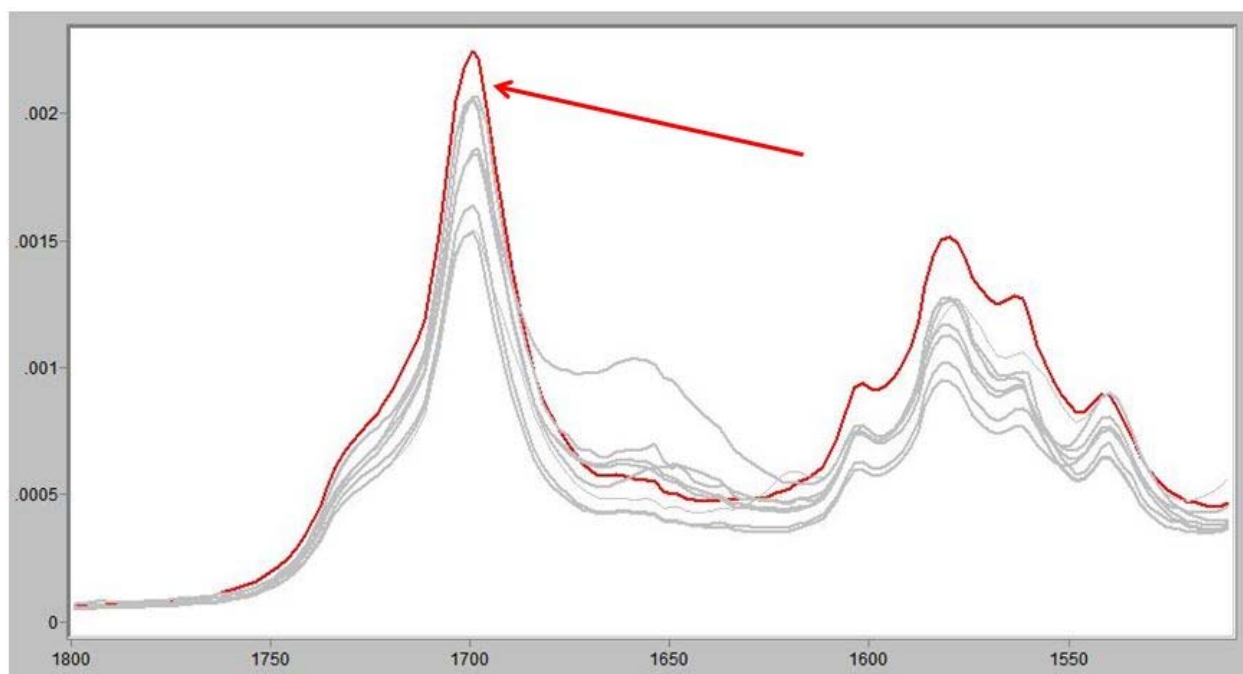


Figure 35. Spectra of authentic (red) and non-authentic samples (except S8) showing the absorption band present due primarily to the API sildenafil citrate (spectra are area normalized).

PCA-CVA showed that it was possible to classify samples based upon their infrared spectrum into eight groups (seven non-authentic and one authentic). HOO-CV was used to determine an estimated error rate of 2.16% using 12 PC's. Figure 36 shows the 3D-scores plot. In this figure, each grouping is colored differently and clustering based upon group assignment in three dimensions is evident. Figure 37 shows the estimated error rates calculated as a function of number of PC's.

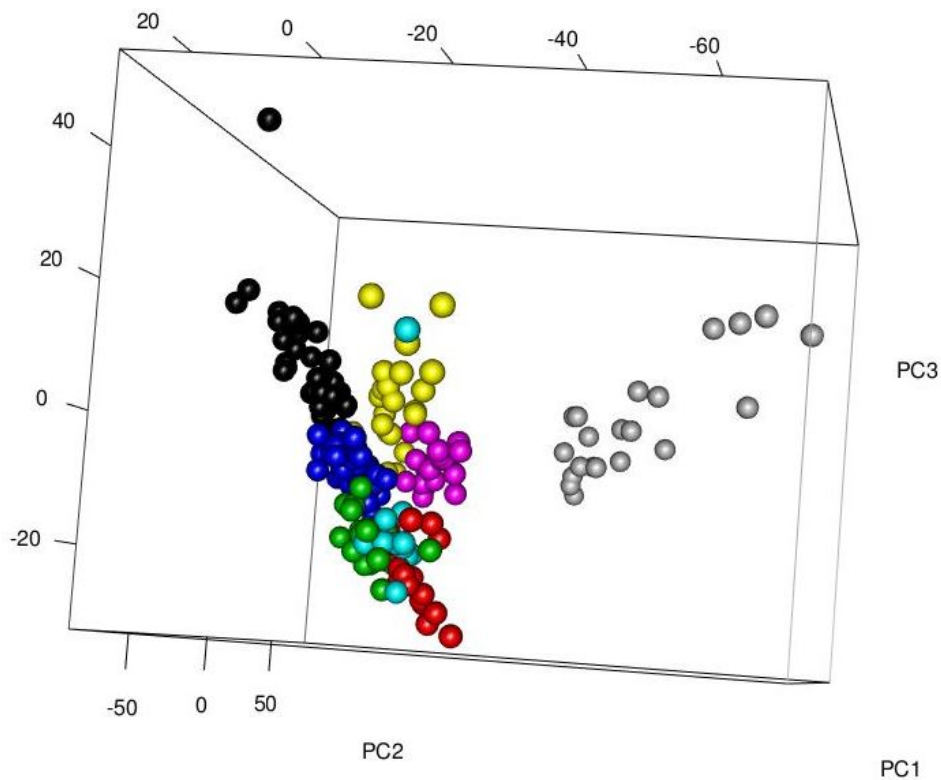


Figure 36. 3D-scores plot of infrared data (autoscaled).

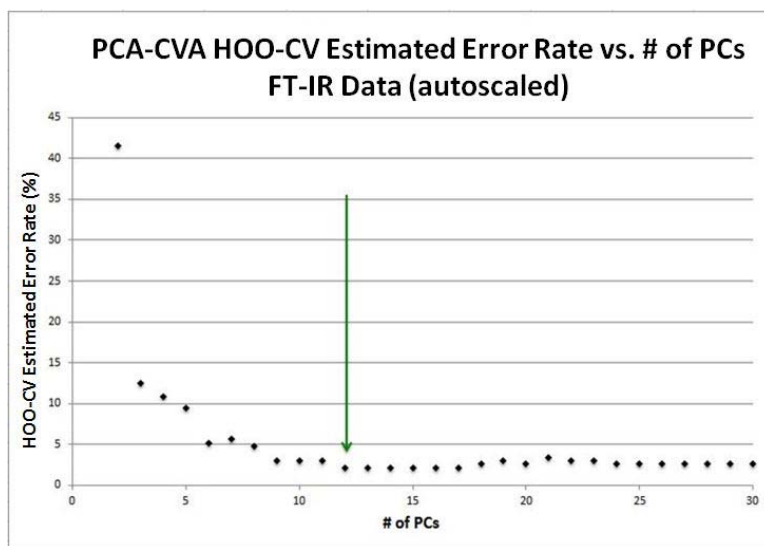


Figure 37. Estimated error rate displayed as a function of the number of PC's. An estimated error rate of 2.16% was observed at 12 PC's.

The HOO-CV classification table is shown in Table 7. This data shows that four of the five misclassifications occurred between groups 2 (sample I1) and 5 (sample I4). The spectra for these two samples are shown in Figure 38. It is clear from these two spectra that the primary difference between these samples as observed in the infrared spectra is in the water content of the samples. The average spectrum of sample I4 contains less water than the average spectrum of sample I1. This is an important observation because infrared analysis is sensitive to water, and drug tablets are known to sorb different amounts of water based upon many factors. For this reason, it is important that when grouping samples together, this fact be considered. In this study, the region of the spectrum sensitive to water was not removed prior to chemometrics analysis because water in pharmaceutical tablets may be present due to amorphous API. Even small amounts of amorphous content can cause the sample to sorb more water than a crystalline form of the drug. (Sacchetti, 2013) Amorphous content may be directly related to manufacturing process (Hancock & Zografi, 1997) and may provide insight as to the source of the tablets.

Table 7. HOO-CV estimated error-rate test results for PCA-CVA analysis of infrared spectra.

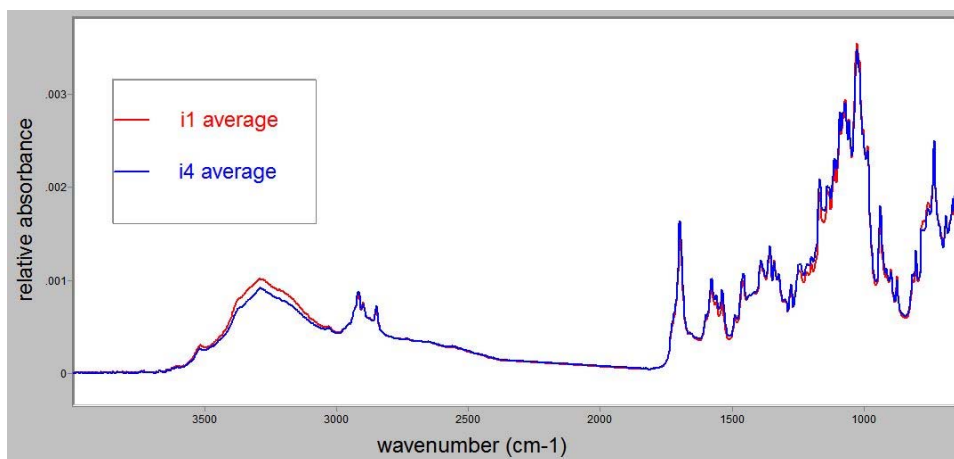


Figure 38. Average infrared spectra of samples I1 and I4 (spectra area normalized).

Summary and Conclusion

This research shows that detection and identification of chemical and physical differences in drug tablets using field-portable infrared spectroscopy provides a chemical signature or profile that may be used to authenticate product. PCA-CVA HOO-CV applied to the infrared data showed that infrared may also be used to differentiate non-authentic samples from each other. This is important because it indicates that infrared analysis performed in the field may be used to establish provenance. A visual comparison of the infrared spectra was used to differentiate non-authentic from authentic samples. Infrared spectra were reproducible within different tablets of the same sample and may be used as a chemical fingerprint of a specific tablet and sample. These spectra may be used to classify samples of unknown origin and provide investigators insight into the sample's manufacturing process and history.

CHAPTER 9. INVESTIGATION AND EVALUATION OF CHEMICAL AND PHYSICAL PROPERTIES OF FINAL DOSAGE FORMS USING RAMAN SPECTROSCOPY

Introduction

The rationale for using Raman spectroscopy to evaluate counterfeit drugs is the same as that for infrared spectroscopy (see chapter 8). The reason it is useful as a complement to infrared spectroscopy is because these two methods have different selection rules. In order for a vibrational mode to be active in the infrared region, the vibration must cause a change in the permanent dipole moment of the molecule. The dipole moment is the product of the charge of the dipole and the charge separation difference. On the other hand, for a vibration to be active in the Raman effect, the polarizability of the molecule must change during the vibration. Polarizability is the value of the induced dipole moment divided by the strength of the field that causes the induced dipole moment. In other words, the electron cloud of the molecule must be more readily deformed in one extreme of the vibration than in the other. (Willard, Merritt Jr., Dean, & Settle Jr., 1988) Due to these differences in selection rules, some samples are more amenable to infrared analysis and some are more amenable to Raman analysis. For instance, samples in an aqueous dispersant may have limited success when analyzed using infrared spectroscopy. This is due to the strong infrared absorption of water which may overwhelm the spectrum and mask the presence of other components in the sample. When analyzed using Raman spectroscopy, water does not generate a strong Raman spectrum and will not usually interfere with the Raman measurement of other components in the sample. On the other hand, samples will frequently exhibit a strong fluorescence signal across the Raman spectrum which may interfere with spectral interpretation and comparison. Raman spectroscopy also may cause problems when analyzing colored (and some non-colored) samples because the sample may

burn. This is because the sample will absorb the light at the laser wavelength. (Arnó, Frunzi, Kittredge, & Sparano, 2014) This energy is dissipated as heat due to non-radiative emissions. (Frunzi, 2014) In these instances, infrared analysis may be more appropriate. Lasers are required for Raman systems in order to generate a sufficient Raman scatter for detection.

Raman has a significant advantage in some applications, though. Raman signal may be directly collected from samples through some transparent glass vials and plastic bags. This capability has likely contributed to its success in field-portable applications. For these reasons, infrared and Raman spectroscopy are considered complimentary techniques. When used together, they can provide information that may enable a more complete understanding of the chemical and physical properties of the samples. (Otieno-Alego & Speers, 2011)

Data generated from Raman analysis can be evaluated many different ways when applied to the analytical challenges associated with counterfeit drugs. In this study, Raman spectra were compared to differentiate authentic from non-authentic samples. Reproducibility of spectra collected from a single tablet, as well as amongst different tablets of the same sample was also evaluated. Samples were classified and the discrimination potential of Raman as a tool for the analysis of counterfeit drugs was evaluated using PCA-CVA HOO-CV.

Experimental Details

Instrumentation

Raman spectra of the core matrices of tablets were collected using a 785L Raman spectrometer (Wasatch Photonics, Durham, NC). Performance of the spectrometer was tested at the start and end of every work day by analyzing cyclohexane and verifying peak position. At all times, the system passed this check. The 785L is a small portable instrument. However, it is not specified for ruggedization. It was used as part of this study primarily due to its size, portability

and performance characteristics. Some of the specifications for this system that are important reasons for its use in this study are shown in Table 8. Figure 39 is an image of the model of Raman instrument used.

Raman 785L Specifications of Importance to this Study	
Compact size	5 in x 6.5 in x 2 in housing
Weight	1.2 kg
Laser type	785-nm single-mode laser, diode stabilized with volume Bragg grating
Diffraction grating	HD 1624 LP/mm volume phase grating
Instrument design	Lens-based spectrograph
<i>f</i>/#	1.3
Interface	USB 2.0
Integration time	1 ms to 2 s
Resolution	10 cm ⁻¹ with 50-μm slit
Sample spot size	<50 μm

Table 8. Raman 785L specifications of importance to this study.



Figure 39. Photograph of Wasatch Raman 785L spectrometer.
(<http://wasatchphotonics.com/systems/vph-spectrometers/raman-flourescence/stroker-785l/>)

Raman Method

Approximately 25 mg of gently ground tablet core were transferred to a small, clear, glass vial. The vial was placed in the vial sample chamber of the spectrometer and its position was adjusted slightly to maximize signal intensity for each measurement. A black drape was placed over the sampling chamber during scanning to minimize stray light. Ten scans were collected with a resolution of 10 cm^{-1} and integration time of 1000 milliseconds for each scan. The instrument's Dash software was used to calculate an average of these ten scans. The laser was then turned off and ten dark scans were collected using the same integration time. The system software was used to calculate the average of these ten scans. The data from the spectrometer including each of the individual scans and the average for both the sample spectra and the dark-scan spectra were then transferred in a single worksheet to Microsoft Excel. Using Microsoft Excel, the dark spectrum average value at each frequency was subtracted from the sample spectrum average value at each frequency. The subtraction values along with their respective frequencies were copied into a new worksheet in Microsoft Excel.

Data Analysis and Chemometrics

The "Excel Exchange" function of Thermo Grams was used to convert this worksheet data into an *.spc file. Each *.spc file created was opened in Thermo Grams and then baseline corrected using a quintic multipoint baseline correction. For each tablet, all spectra were averaged using the array basic "average" function in Grams. For each sample, all spectra from each tablet of the sample were averaged using the array basic "average" function in Grams. The chemometric methods of PCA and CVA were applied to investigate the classification and discrimination power of Raman spectroscopy. Non-authentic samples were sorted into seven groups based upon physical appearance, dimensions, and receipt date; authentic samples were

categorized into a single group. The deconvolution data, specifically the peak positions and areas, also were analyzed using HOO-CV PCA-CVA to determine an estimated error rate for the classification of sildenafil citrate tablets.

Results and Discussion

It was possible to differentiate the authentic samples from all non-authentic samples using Raman spectroscopy. In most cases, differences in spectra were small but reproducible. Using PCA-CVA, 3D-scores plots were created and visual separation of samples was not evident in these plots. Although separation was not evident in three dimensions for the Raman data, the estimated error rate calculated using HOO-CV was lower than it was for the infrared data and calculated to be 0.56% using 14 PC's. This lower estimated error rate indicates that Raman analysis may be just as useful as infrared analysis to establish provenance. Not only can Raman be used to differentiate authentic from non-authentic samples, but it also may be used to sort non-authentic samples and ultimately lead to the establishment of provenance. Figure 40 shows the average spectra collected from two different samples of authentic VIAGRA. These spectra are consistent with each other. The same bands and were present in each sample across the Raman spectrum with very similar band intensities.

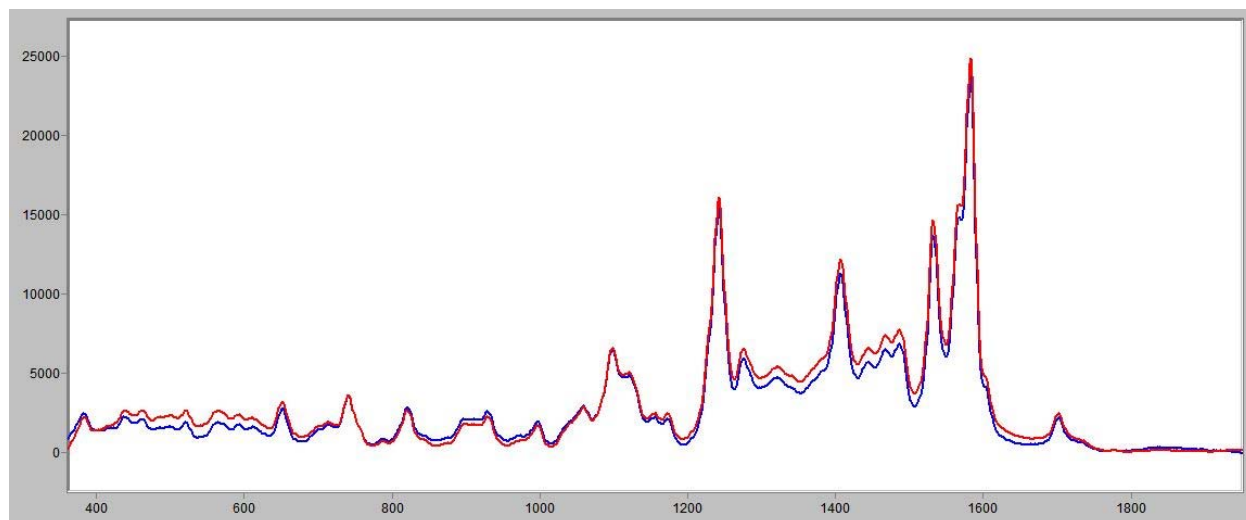


Figure 40. Raman spectral averages of samples S15 (red) and S16 (blue). Both samples are authentic VIAGRA.

Figures 41 through 49 show the average Raman spectrum of an authentic sample compared with the average spectrum from each of the nine non-authentic samples. Note that the differences between the authentic and non-authentic samples were relatively small. This indicates that the chemical composition of the non-authentic samples was similar but not identical to the chemical composition of the authentic samples. However, the spectra collected from different tablets of the same sample were consistent with each other. It was possible to differentiate all non-authentic samples from the authentic samples.

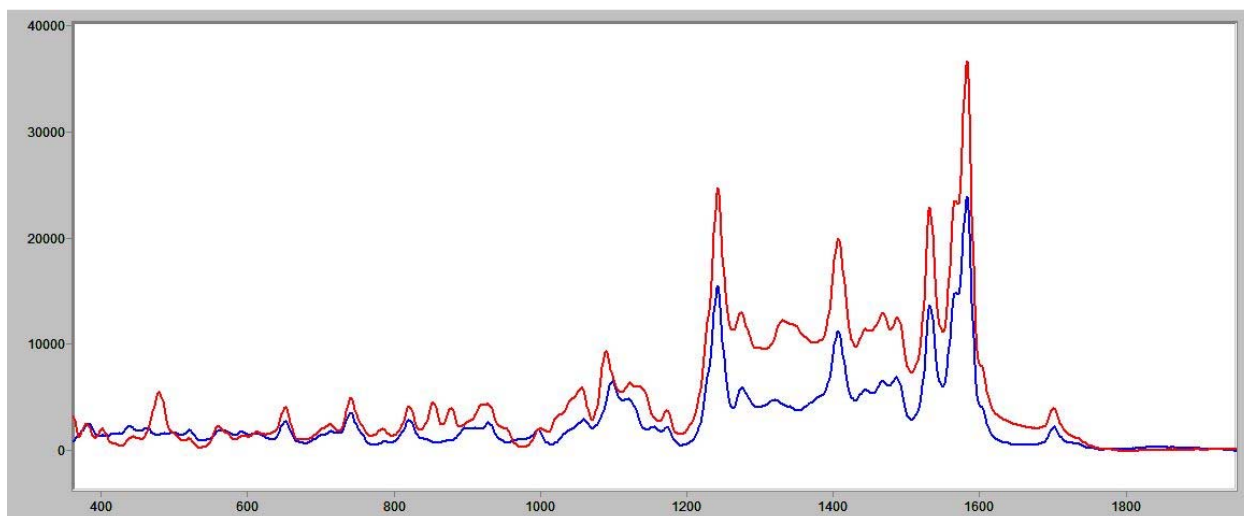


Figure 41. Raman spectrum of authentic sample (blue) compared with non-authentic I1 (red).

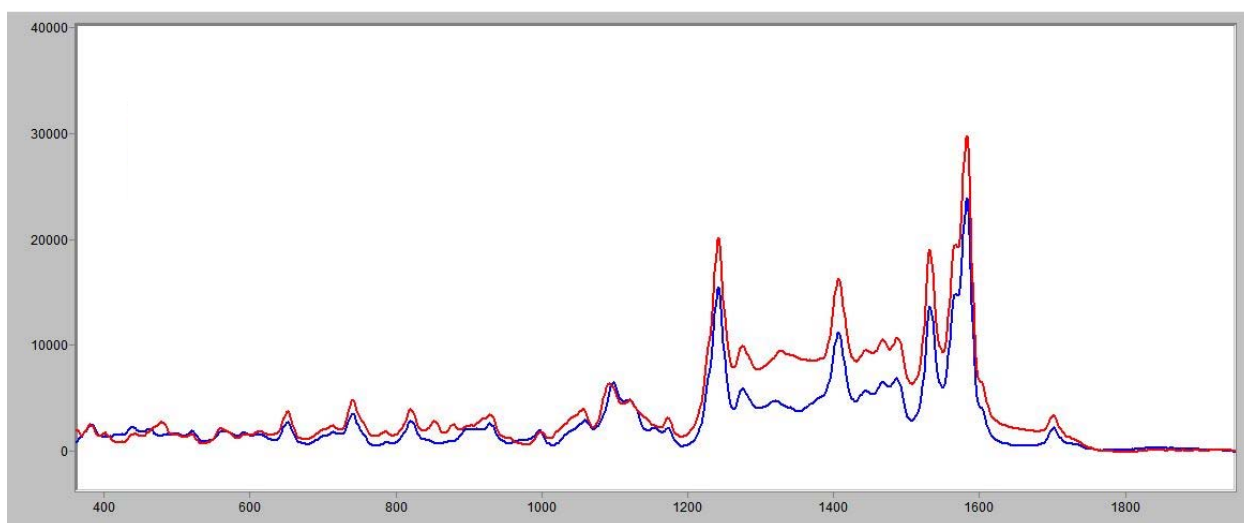


Figure 42. Raman spectrum of authentic sample (blue) compared with non-authentic I2 (red).

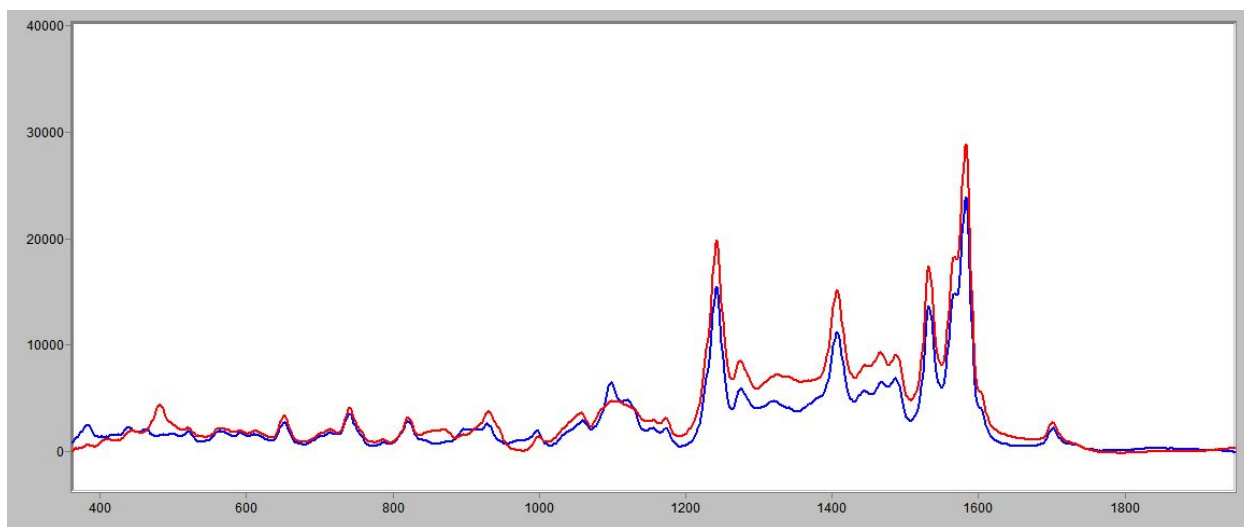


Figure 43. Raman spectrum of authentic sample (blue) compared with non-authentic I3 (red).

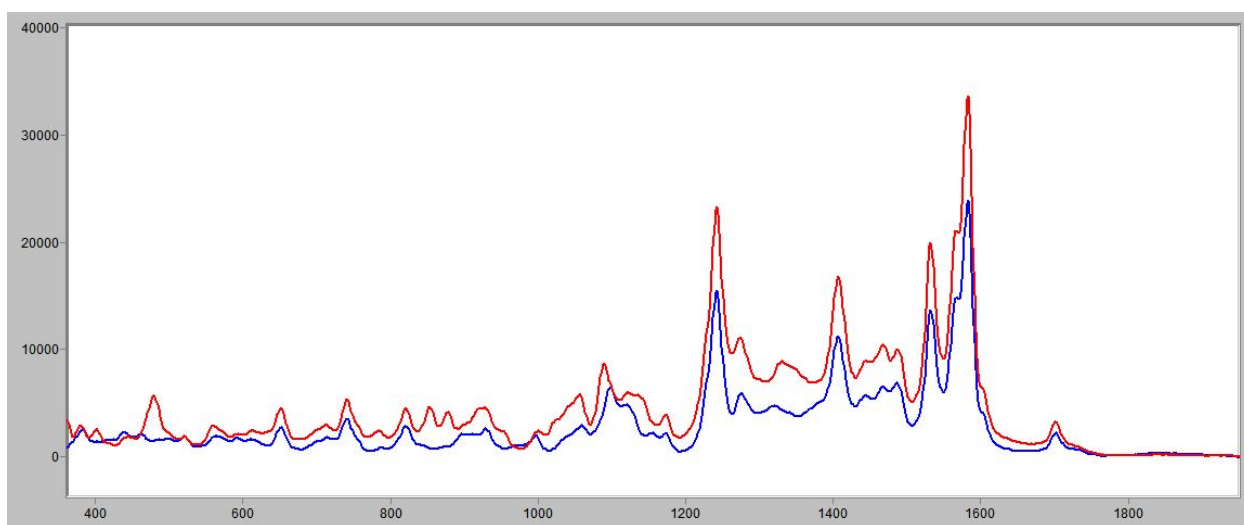


Figure 44. Raman spectrum of authentic sample (blue) compared with non-authentic I4 (red).

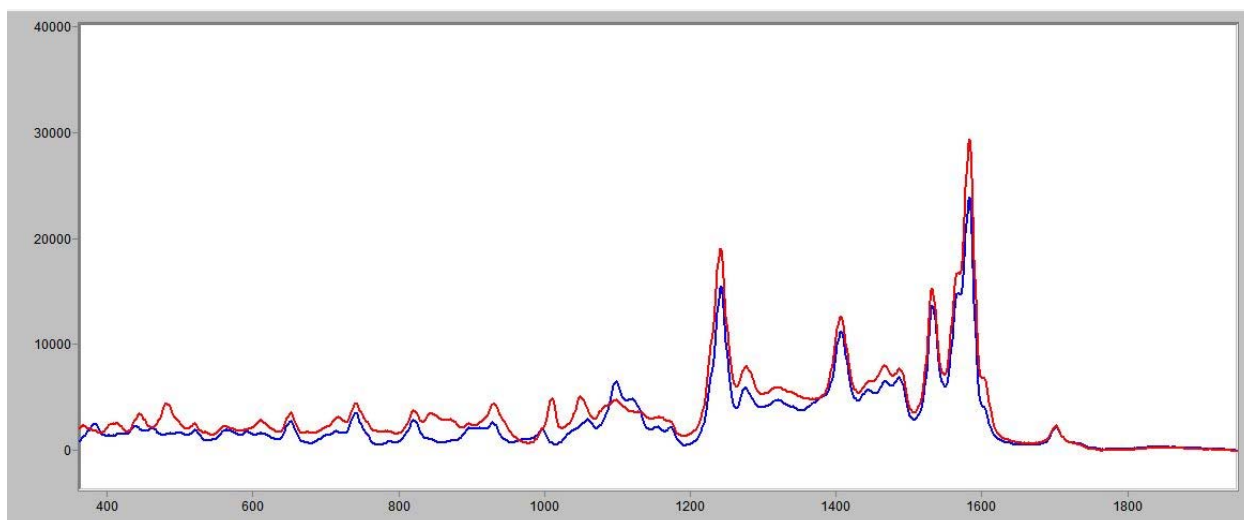


Figure 45. Raman spectrum of authentic sample (blue) compared with non-authentic I5 (red).

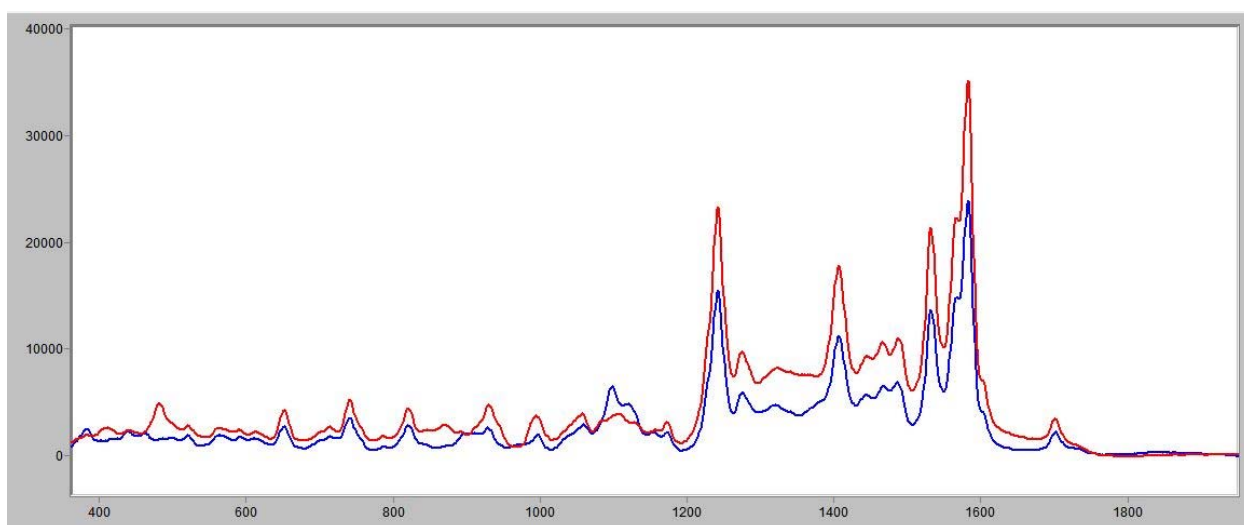


Figure 46. Raman spectrum of authentic sample (blue) compared with non-authentic S7 (red).

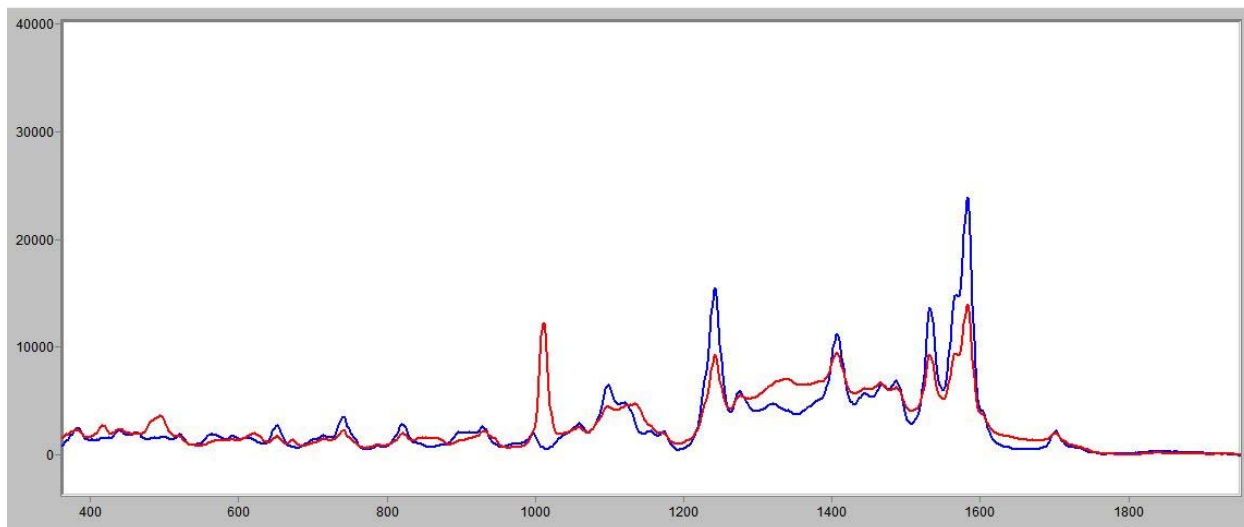


Figure 47. Raman spectrum of authentic sample (blue) compared with non-authentic S8 (red).

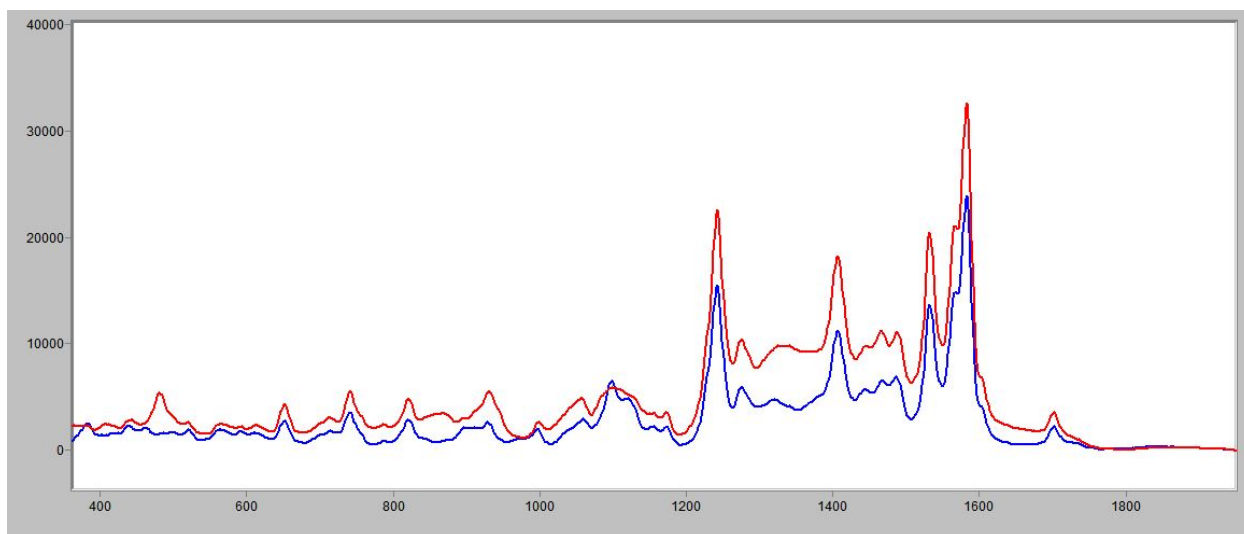


Figure 48. Raman spectrum of authentic sample (blue) compared with non-authentic SING1 (red).

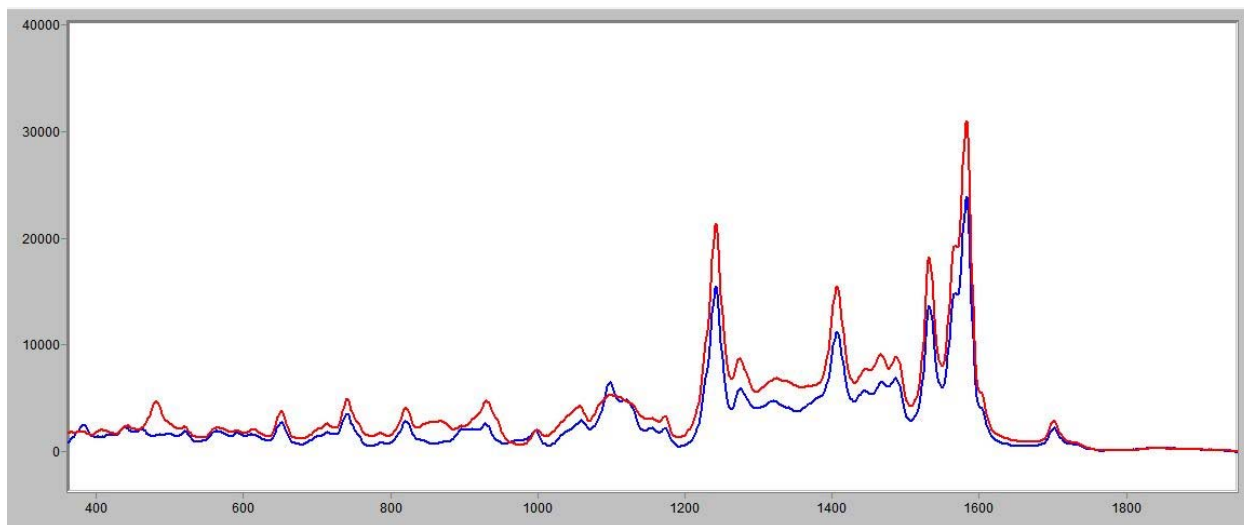


Figure 49. Raman spectrum of authentic sample (blue) compared with non-authentic SING2.

Although only the average spectrum for each sample is shown in the preceding nine figures, all of the spectra collected from each tablet and from the same sample were consistent with each other. There was some variance in the intensities of some of the Raman bands within a sample, but there wasn't a single instance where two spectra from the same sample contained different Raman bands.

PCA-CVA showed that it was possible to classify samples based upon their Raman spectrum into eight groups (seven non-authentic and one authentic). HOO-CV was used to determine an estimated error rate of 0.56% using 14 PC's.

Figure 50 shows the 3D-scores plot from PCA-CVA. In this figure each group is colored differently and, unlike with the infrared spectra where clustering based upon group assignment was evident in three dimensions, no clustering is observed in the Raman data. However, figure 51 shows the estimated error rates calculated as a function of number of PC's for the Raman, and even though clustering is not evident in three dimensions, Raman spectroscopy was capable of successfully classifying most samples. This difference in clustering observed in the 3D-scores

plots between the infrared (figure 36) and the Raman data (see figure 50) is interesting. It is possible that the reason the separation was not evident in the 3D-scores plot for the Raman data is because the Raman analysis spot size ($50\text{ }\mu\text{m}$) is significantly smaller than it is for the infrared analysis ($1.3\text{ mm} \times 0.8\text{ mm}$), but this hypothesis was not tested.

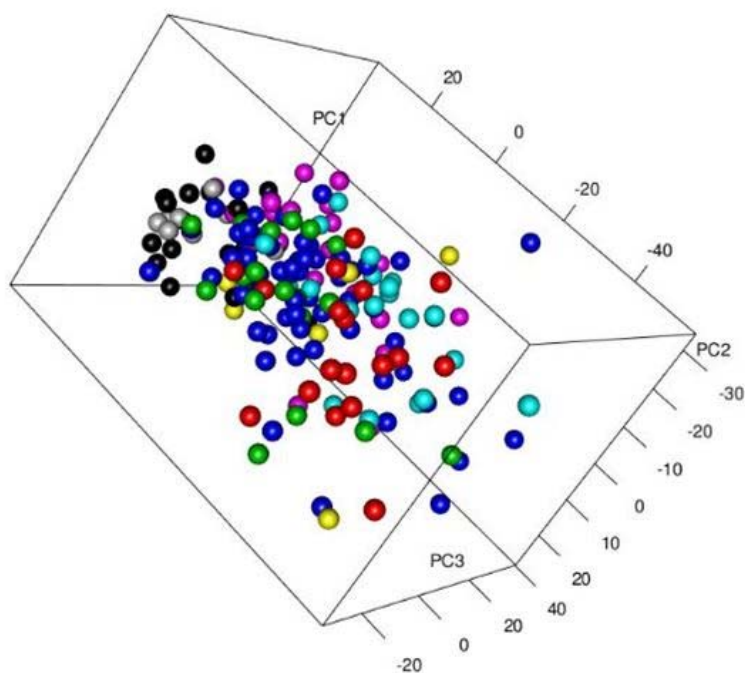


Figure 50. 3D-scores plot of Raman data (autoscaled).

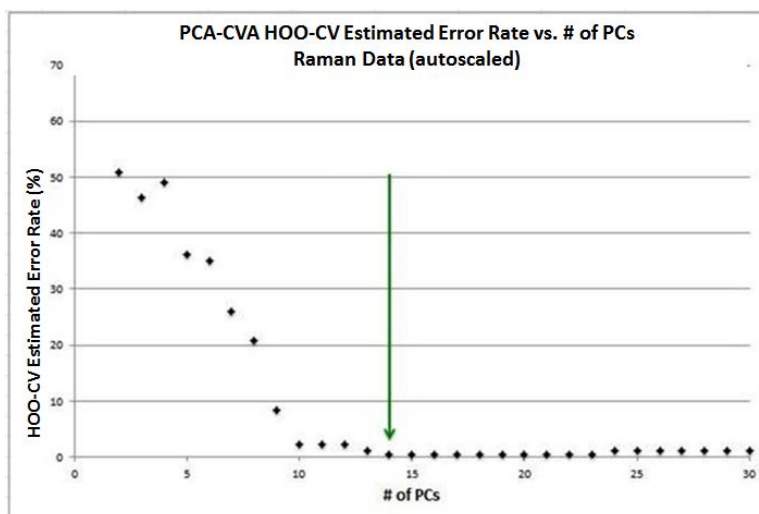


Figure 51. Estimated error rate displayed as a function of the number of PC's. An estimated error rate of 0.56% was observed at 14 PC's.

Summary and Conclusion

This research shows that detection and identification of chemical and physical differences in drug tablets using field-portable Raman spectroscopy provides a chemical signature or profile that may be used to authenticate product. PCA-CVA HOO-CV applied to the Raman data showed that Raman may be used to distinguish authentic from non-authentic samples, and to differentiate non-authentic samples from each other. This is important because it indicates that Raman analysis performed in the field may be used to establish provenance. A visual comparison of the Raman spectra was used to differentiate non-authentic from authentic samples. Raman spectra were reproducible within different tablets of the same sample. These spectra may be used to classify samples of unknown origin and provide investigators insight into the sample's manufacturing process and history. For example, differences in spectra may result from differences in solid-state form of the active or inactive ingredients that are produced during manufacture or storage, or may be have different ingredients present that could be linked to manufacturer.

CHAPTER 10. INVESTIGATION AND COMPARISON OF ORGANIC VOLATILES AND RESIDUAL SOLVENTS IN DRUG PRODUCTS USING GAS CHROMATOGRAPHY-MASS SPECTROMETRY

Introduction

When pharmaceutical tablets are manufactured, chemicals are present in the finished tablet at trace levels. These chemicals are introduced into the tablet in a variety of ways. They may be present in the raw materials, they may be solvent residues remaining after tablet manufacture, or they may even be degradation products that develop during manufacture or storage. These trace chemicals generate a chemical fingerprint that is representative of the tablet. They also provide insight about the tablet's manufacture and storage.

When manufacturing processes are well controlled and adhere to regulatory guidelines as is typical for an authentic product, this chemical fingerprint is well controlled and reproducible. The ability to detect and identify these chemicals in a reliable manner is useful, providing a chemical fingerprint that is representative of the authentic product and may be used to differentiate authentic from non-authentic tablets. This chemical fingerprint may also be used to classify counterfeit drugs, providing investigative leads useful in establishing source or origin.

GC-MS is useful for detecting and identifying these trace chemicals. Data generated from this type of analysis can be evaluated many different ways when applied to the analytical challenges associated with counterfeit drugs. In this study, total ion chromatograms were compared to determine reproducibility amongst different tablets of the same sample. In addition, they were used to differentiate authentic from non-authentic samples. Samples were heated and organic volatiles and residual solvents evolved from the sample were collected and analyzed.

Experimental Details

Instrumentation

GC-MS data were collected using a GUARDION™ GC-MS (Smiths Detection, Danbury, CT). The system uses a 5-m long MXT®-5 (Restek Corporation, Bellefonte, PA) resistively heated capillary column (inner diameter 0.1 mm, film thickness of 0.4 µm). This column is a crossbond® diphenyl/dimethylpolysiloxane column. The carrier gas is helium (Leland, South Plainfield, NJ) introduced via disposable canister. Sample collection and introduction to the GUARDION was performed via solid-phase microextraction (SPME). A CUSTODION® (Torion Technologies, American Fork, UT) SPME holder was used with a Supelco (St. Louis, MO) 23-gauge, 65 µm DMS/DVB fiber assembly.

Performance of the system was tested at the start and end of every work day and periodically throughout the day. Performance testing evaluates both GC and MS performance. To perform this testing, a standard containing 13 chemicals is analyzed. These 13 chemicals have expected retention-time values between 0 and 90 seconds and are spaced across this range. GC performance acceptance criteria required that the retention times for all 13 chemicals must be the stated +/- 2 seconds. Retention-time values measured during all performance testing were always within the accepted range. Table 9 shows the expected retention-time values for these 13 chemicals.

Chemical in Standard	CAS Number	Stated Retention-Time Value (s)
Acetone	67-64-1	11.34
Methylene chloride	75-09-2	13.26
Methyl-t-butyl ether	163-40-44	15.17
Heptane	142-82-5	26.25
Methylcyclohexane	108-87-2	28.92
Toluene-d8	2037-26-5	32.85
Perchloroethylene	127-18-4	37.34
Bromopentafluorobenzene	344-04-7	41.84
Bromoform	75-25-2	45.14
1,2-Dibromotetrafluorobenzene	827-08-7	65.94
Methyl salicylate	119-36-8	72.25
Tetrabromoethane	79-27-6	79.83
Tetradecane	629-59-4	85.76

Table 9. Chemicals contained within standard sample analyzed during performance testing.

In addition to evaluating the GC, performance testing also evaluates MS performance. MS performance includes tests for spectral quality, mass calibration, mass resolution, ion statistics, space charge, signal-to-noise ratio, and sensitivity. The performance-test procedure used was the procedure recommended by the instrument manufacturer. The system did not always pass performance-test criteria. However, the reasons for all failures were due to MS performance. Spectral data, however, were not directly interpreted and compared. Only GC retention-time data was used for comparison.

The GUARDION is specifically intended for field use. Some of the specifications for this system, especially those intended to support portability and ruggedization of the instrument, are shown in Table 10. An image of the model of GC-MS instrument used is shown in figure 52.

GUARDION Specifications of Importance to this Study	
Compact size	15.5 in x 15 in x 9 in excluding handle
Weight	14.6 kg
GC column	MXT-5 column, 5 m, 0.1 mm inner diameter, 0.4 μ m film thickness
Carrier gas	Helium carrier gas supply, internal disposable cartridge
Mass spectrometer	Toroidal ion trap
Vacuum system	Turbomolecular vacuum pump with diaphragm roughing pump
Sample collection	Solid-phase microextraction
Hot-zone operation	Sealed for operation in the hot zone
Decontamination	Spray/wipe down
Operating temperature	0°C to 45°C
Operating humidity	0% - 95%
User interface	Embedded software with touch-screen
Data export	Full USB support; Ethernet capable; mouse and keyboard capable
Power	Removable, rechargeable Li-ion battery; external power supply
Mass range	43 m/z - 500 m/z
Temperature programming	Up to 300°C

Table 10. GUARDION specifications of importance for its use in this study.



Figure 52. GUARDION GC-MS. Photograph courtesy of Smiths Detection, Danbury, CT.

Method

Samples were analyzed using a field-portable toroidal ion-trap GC-MS. Samples were injected directly from the SPME holder into the inlet of the GC-MS. During analysis, samples elute directly from the GC into the ion trap of the MS. Ionization occurs via electron impact at 70 eV. The carrier gas used was helium. The injector and transfer line temperatures were 270°C. The column temperature was held at 50°C for 10 seconds and then ramped at a rate of 2°C per second to 296°C. The temperature was held at 296°C for 47 seconds. The voltage of the MS was scanned continually to detect mass fragments in the range between 43 and 500 atomic mass unit's. Scan time was approximately 60 milliseconds and continuously performed throughout the GC analysis.

To prepare for GC-MS analysis, each tablet was gently crushed and transferred to a GC-MS headspace vial. Samples were heated to 60°C and held at this temperature for 20 minutes. The headspace was then sampled at 60°C for five minutes using the SPME technique. The

sample was then injected directly from the SPME holder into the inlet of the GC-MS. Sampling and analysis was performed two times in immediate succession. The first sampling used a PDMS/DVB SPME sorbent; the second sampling used a carboxen SPME sorbent. Samples were then heated to 110°C and held at this temperature for 20 minutes. The same SPME headspace sampling and analysis steps performed at 60°C were repeated at 110°C. In some instances, SPME headspace sampling was performed using only a PDMS/DVB SPME sorbent. The reason both fibers were not always used is because, initially during data collection, the PDMS/DVB SPME sorbent was used in duplicate to verify reproducibility. The carboxen fiber was not used during these earlier experiments. After reproducibility was observed in the first samples analyzed, it was deemed to be more important to evaluate the use of the carboxen sorbent during the second injection rather than continue to verify reproducibility.

Results and Discussion

It was possible to differentiate the authentic samples from all non-authentic samples using this method. In most cases, differences in chromatograms, i.e., chemical fingerprints, between the authentic and the non-authentic sample were significant. An attempt was made to average chromatograms to enable quantitation of these visual observations. Due to many instrumental factors including the dynamic ionization that occurs in the instrument during sample analysis to optimize MS results, retention-time values from one run to the next are unique. This makes an averaging function impossible to perform without changing retention-time values. It was determined that averaging chromatograms would not be performed.

Figures 53 through 61 show the chromatogram of an authentic tablet compared with a chromatogram from each of the nine non-authentic samples. A chromatogram (in this context) is a display showing all of the chemicals detected during GC-MS analysis. The x-axis represents

the analyte's retention time, and the y-axis represents abundance. This study was non quantitative, so although relative abundances within a single chromatogram may be used as a factor to be evaluated within that single chromatogram, no quantitative assessment of each analyte's concentration within the tablet was or should be performed. Ideally, each peak in the chromatogram is representative of a chemical present in the sample. In this study, the nature of the peak was not important and overlapping peaks were not considered to be a problem. The presence or absence of a peak at a specific retention time was the criteria used for discrimination.

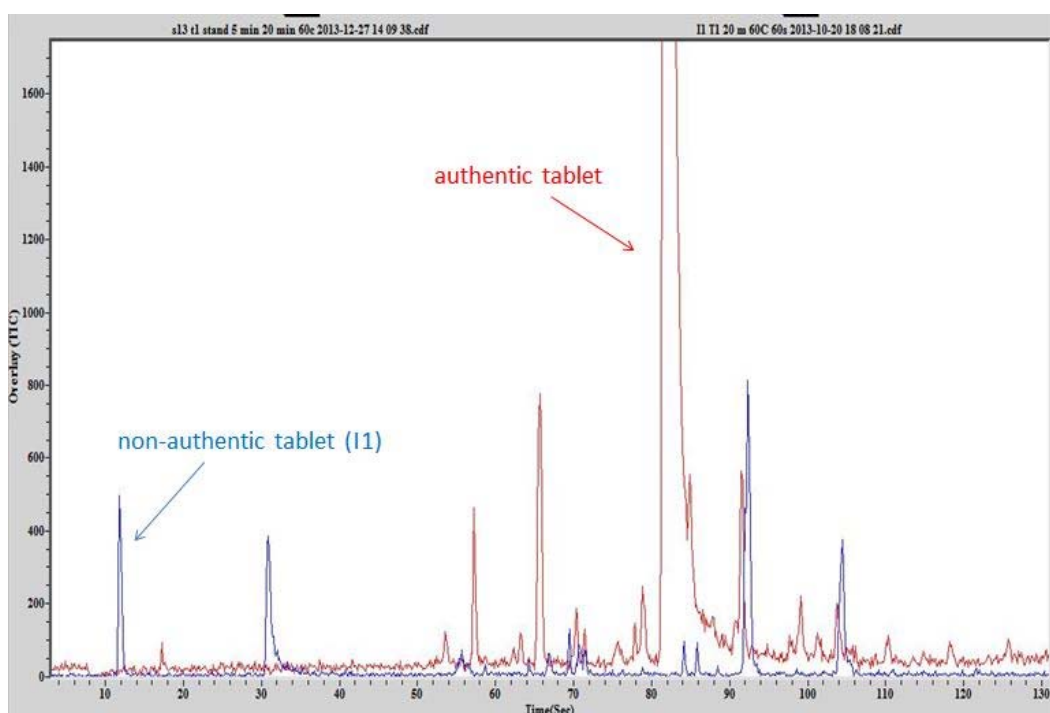


Figure 53. Chromatogram of authentic sample compared with non-authentic I1 (PDMS/DVB SPME sorbent, 60°C).

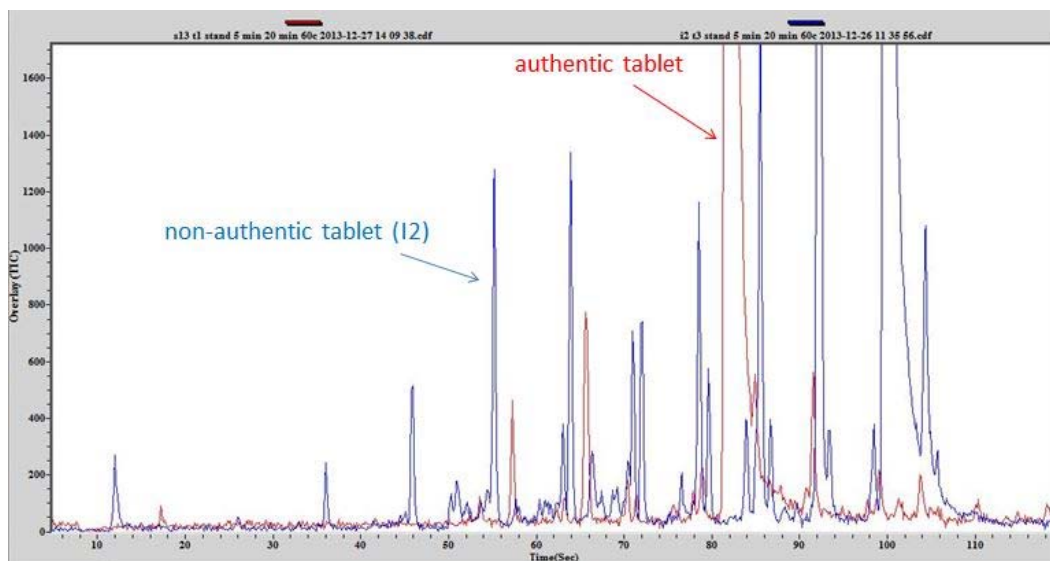


Figure 54. Chromatogram of authentic sample compared with non-authentic I2 (PDMS/DVB SPME sorbent, 60°C).

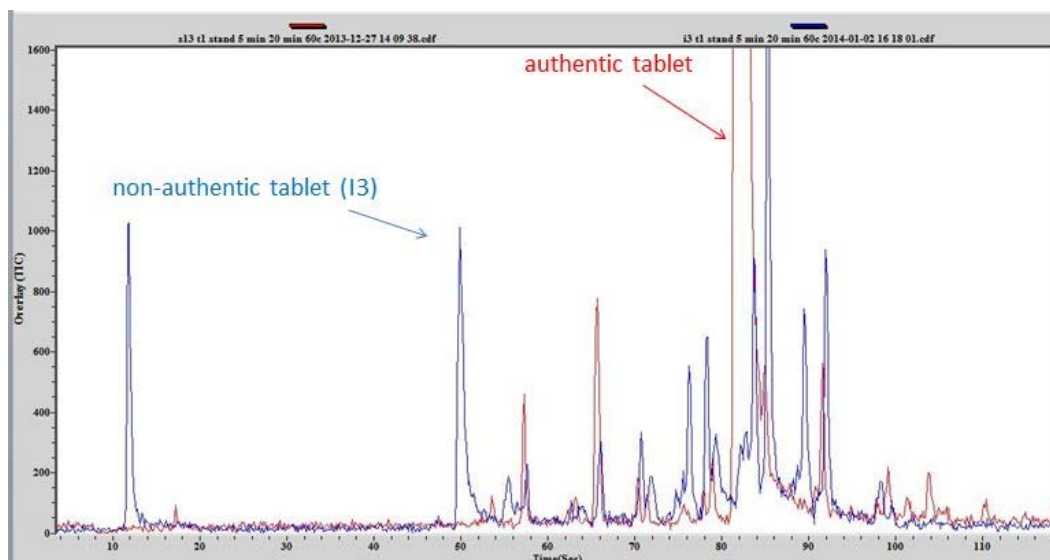


Figure 55. Chromatogram of authentic sample compared with non-authentic I3 (PDMS/DVB SPME sorbent, 60°C).

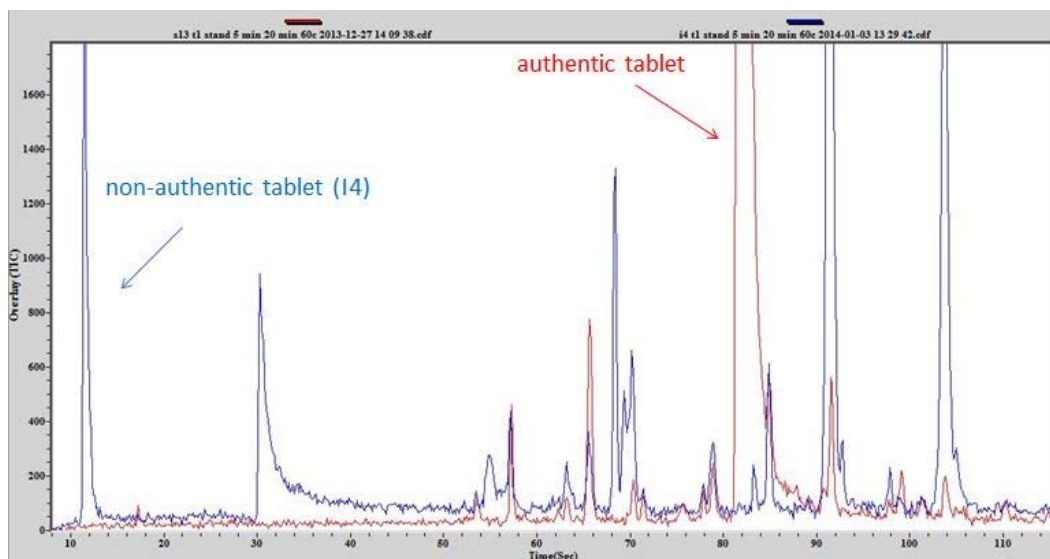


Figure 56. Chromatogram of authentic sample compared with non-authentic I4 (PDMS/DVB SPME sorbent, 60°C).

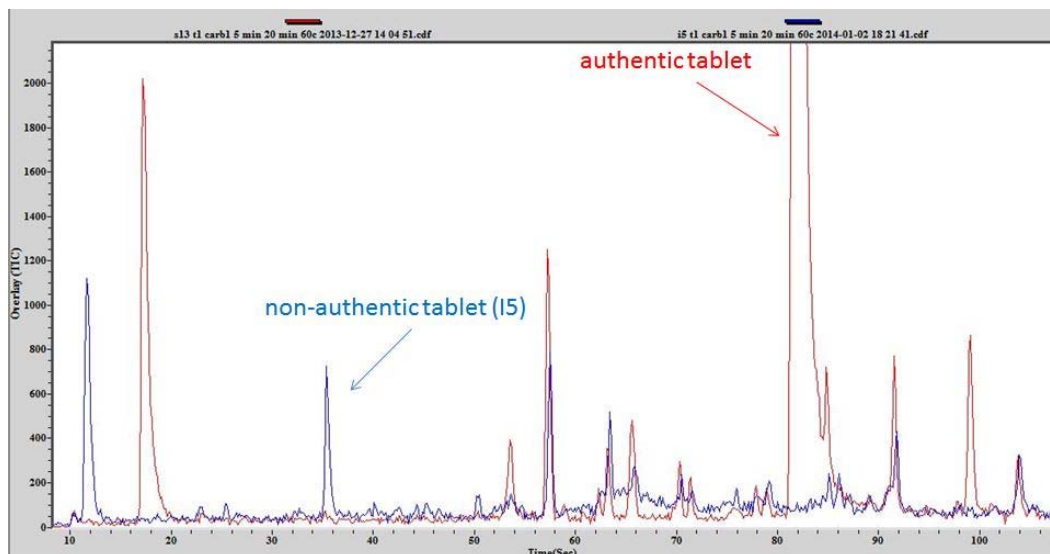


Figure 57. Chromatogram of authentic sample compared with non-authentic I5 (PDMS/DVB SPME sorbent, 60°C).

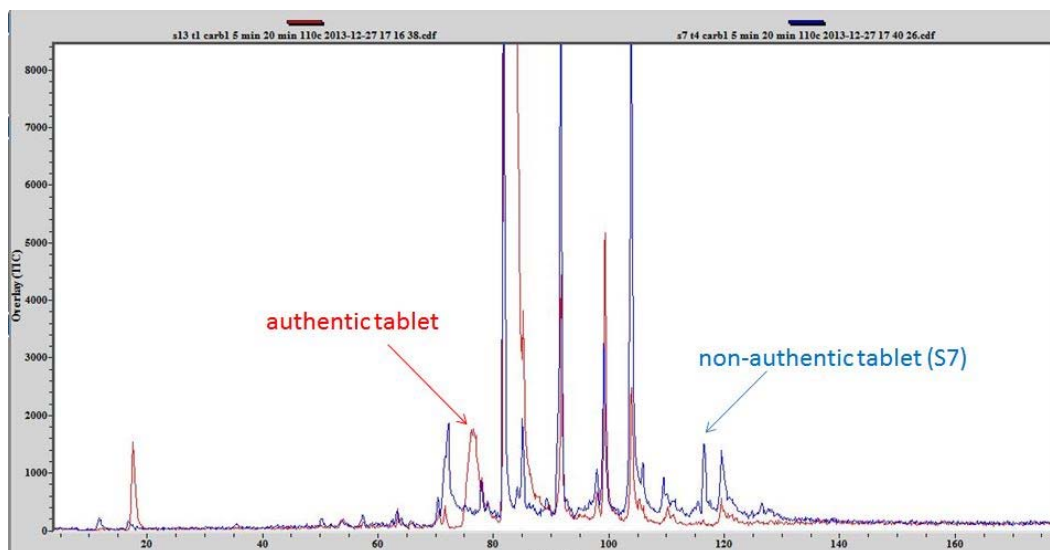


Figure 58. Chromatogram of authentic sample compared with non-authentic S7 (PDMS/DVB SPME sorbent, 60°C).

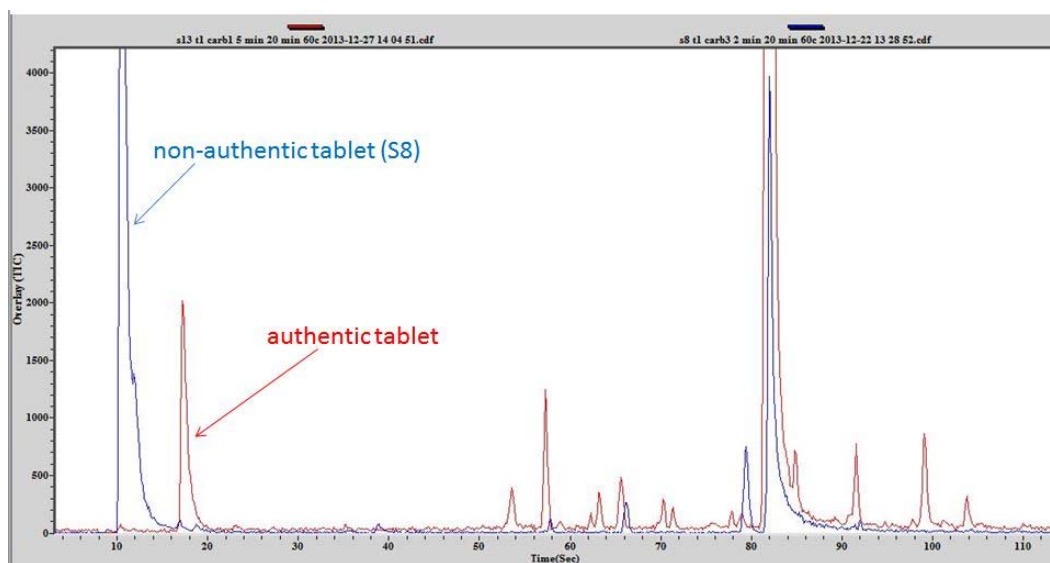


Figure 59. Chromatogram of authentic sample compared with non-authentic S8 (PDMS/DVB SPME sorbent, 60°C).

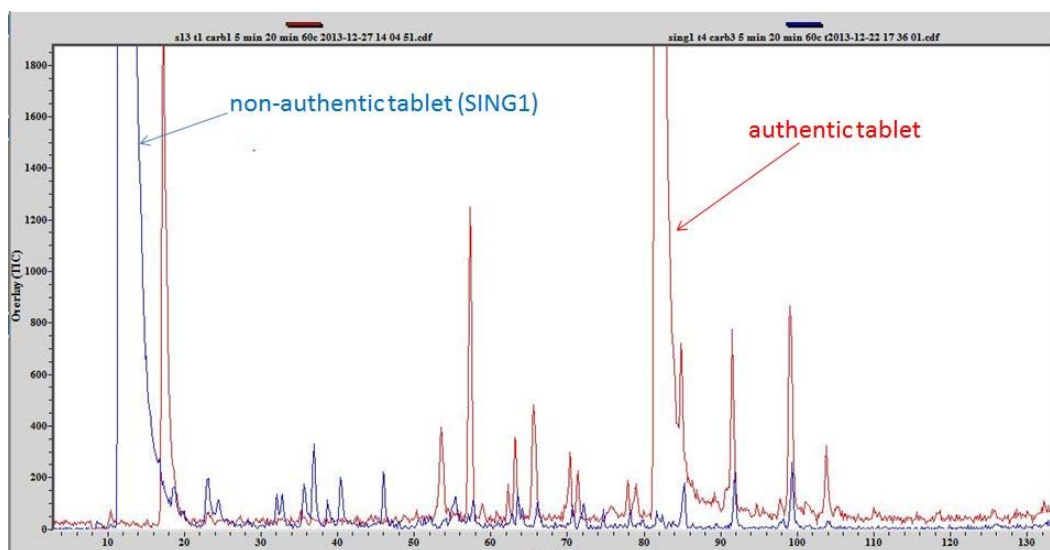


Figure 60. Chromatogram of authentic sample compared with non-authentic SING1 (PDMS/DVB SPME sorbent, 60°C).

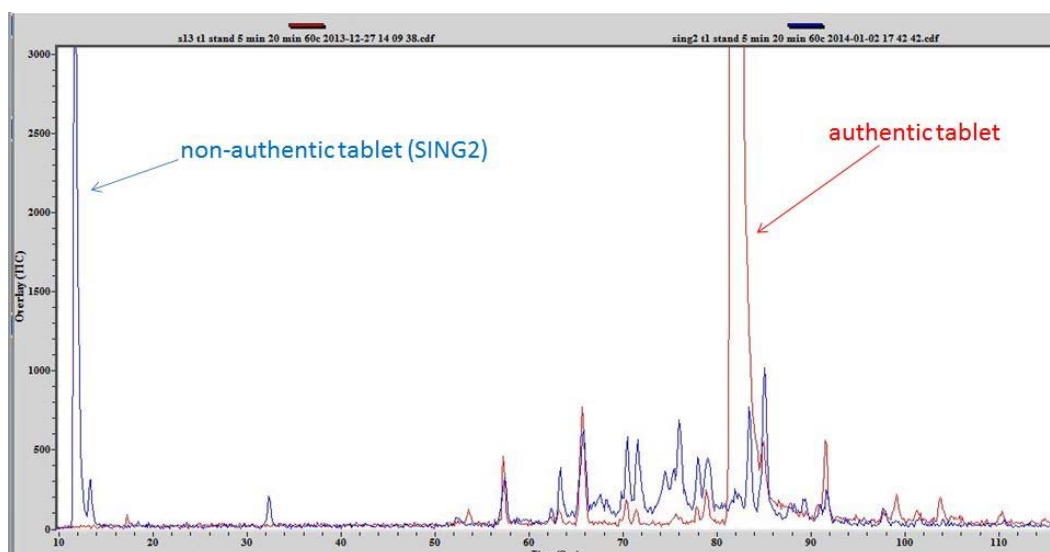


Figure 61. Chromatogram of authentic sample compared with non-authentic SING2 (PDMS/DVB SPME sorbent, 60°C).

Although only a single chromatogram for each sample is shown in the preceding nine figures, it is important to note that all chromatograms generated from each tablet within a sample were compared to each other. In all cases, the chromatogram of each sample was generally consistent from tablet to tablet, but was dependent upon SPME sorbent and sample temperature.

Therefore, only results generated using the same SPME sorbent and sample temperature were used for differentiation.

Figure 62 shows an overlay of seven chromatograms from seven different tablets of the same sample collected using the same SPME sorbent and sample temperature (PDMS/DVB SPME sorbent, 60°C). Although peak heights are variable from tablet to tablet, the general pattern is consistent across the tablets analyzed. This type of chromatogram reproducibility was typically observed for different tablets of a given sample analyzed using the same conditions.

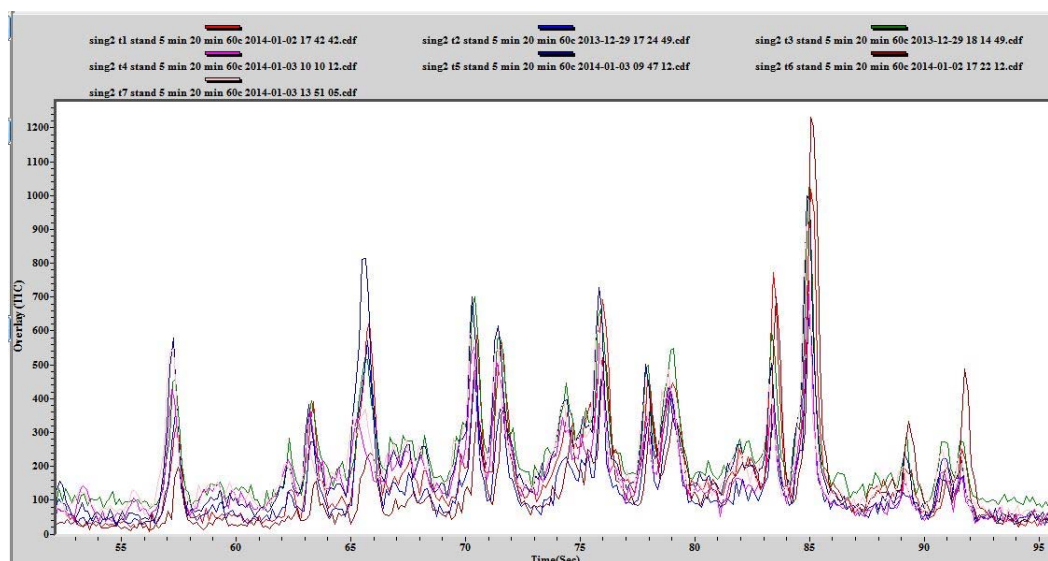


Figure 62. Seven chromatograms of seven tablets of sample SING2. Sampling was performed using PDMS/DVC SPME sorbent at 60°C.

Chromatogram differences based upon SPME sorbent are expected. Different SPME sorbents, by design, selectively sorb different chemicals differently. This selective sorption accounts for the differences in chromatograms from the same tablet analyzed at the same temperature using different SPME sorbents. As an example, Figure 63 shows the chromatograms for sample SING2 collected using two different sorbent materials analyzed at the same temperature and under otherwise identical conditions. Note that the peak intensities for

some chemicals across the chromatogram are different. The most significant differences are observed for chemicals with lower boiling point which elute at lower retention times on this GC column. The carboxen fiber is a more aggressive sorbent for these types of chemicals, generating patterns with higher concentrations of these chemicals in the chromatogram from the same sample analyzed under otherwise identical conditions. Figure 64 shows replicate analysis from the same tablet analyzed under the same conditions using the same SPME sorbent. Note that peak intensities are much more consistent across the entire chromatogram when replicate analysis using the same sorbent materials was performed. These figures show typical behavior observed across all samples analyzed.

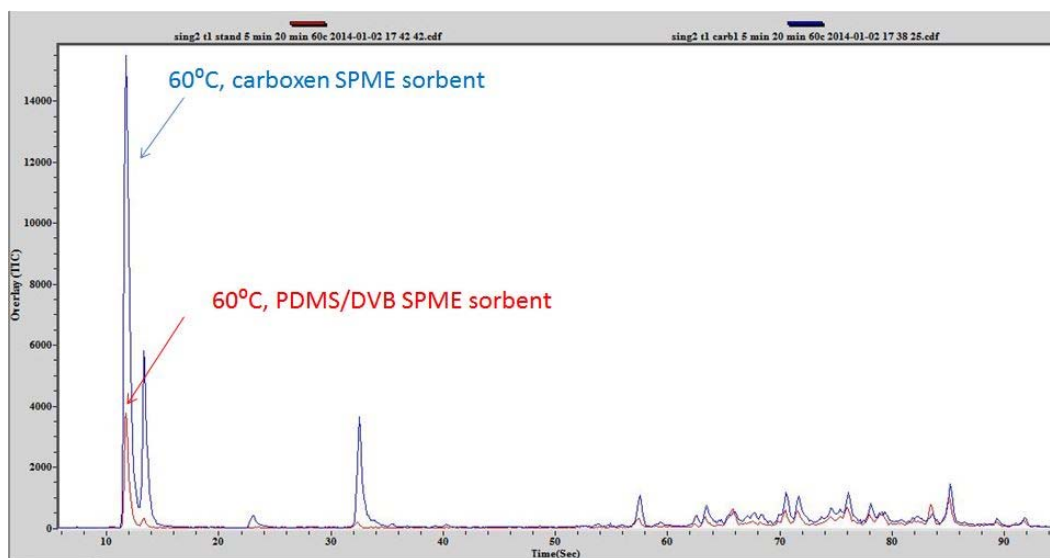


Figure 63. Chromatograms of tablet 1 of sample SING2 analyzed at the same temperature (60°C) using two different SPME sorbents (PDMS/DVB and carboxen).

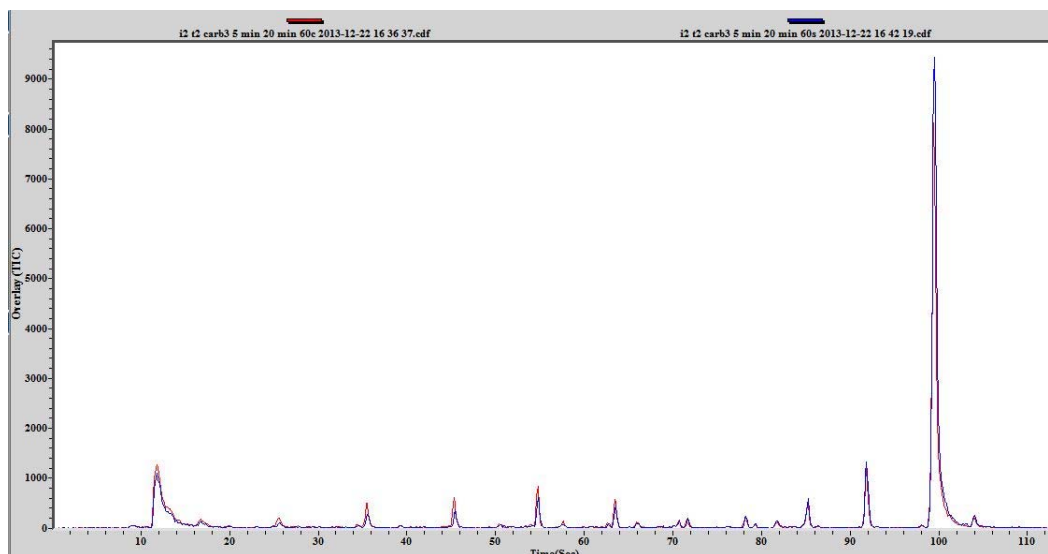


Figure 64. Chromatograms of tablet 2 of sample I2 analyzed at the same temperature (60°C) using the same SPME sorbent (carboxen).

Differences in chromatograms based upon sample temperature are also expected. Temperature will modify the chemical composition of the headspace and, therefore, the resulting chromatogram. Figures 67 shows the types of differences that may be observed based upon sampling temperature. Chromatograms for sample SING2 collected from the same tablet at 60°C and 110°C using the PDMS/DVB SPME sorbent are displayed. Although there is varying peak intensities across the chromatograms, the most significant differences lie in the region at retention times greater than about 90 seconds, where chemicals present at 110°C are completely absent in the 60°C sample. This type of difference based upon temperature was consistent whether comparisons were made using PDMS/DVB SPME sorbent or carboxen sorbent.

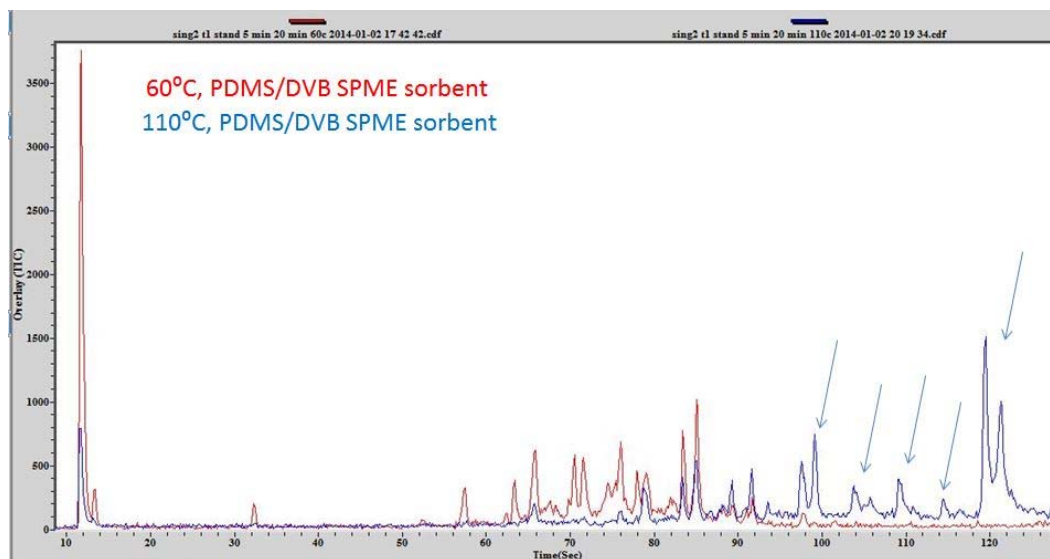


Figure 65. Chromatograms of tablet 1 of sample SING2 analyzed at different temperatures (60°C and 110°C) using the same SPME sorbent (PDMS/DVB).

Summary and Conclusion

This research shows that detection and identification of organic volatiles and residual solvents in drug tablets using field-portable GC-MS provides a chemical signature that can be used to authenticate product. A visual comparison of the chromatograms produced by these samples made this a relatively trivial task. Chromatograms were reproducible within different tablets of the same sample and may be used as a chemical fingerprint of a specific tablet and sample. These chemical fingerprints may be used to classify samples of unknown origin and provide investigators insight into the sample's manufacturing process and history.

CHAPTER 11. AN ANALYTICAL SCHEME FOR TESTING OF SUSPECTED COUNTERFEIT TABLETS IN THE FIELD

The data summarized in the preceding chapters shows that differentiating authentic from non-authentic samples using many different analytical methods in the field is possible. The choice of method to be used is dependent upon the sample. In some instances, a visual comparison between the authentic and non-authentic samples will suffice. In others, chemical methods must be used to attempt differentiation. It may be prudent, though, when analyzing suspected counterfeit drugs in the field, to measure samples using a combination of methods regardless of whether or not a non-authentic sample is detected during the initial examination. This is because although individual methods may be used independently to show that a suspect sample is not authentic, the real challenge facing forensic scientists is in the sourcing of these goods.

It seems that any attempt at sourcing requires access to data from many different samples in order to identify patterns in the data collected from non-authentic samples. There is a need for a database of these samples. Data collected quickly in the field at border crossings and other law-enforcement venues can provide the content for this database and be easily saved in an electronic format for review at a later time by members of forensic science and law-enforcement organizations. It is important that the methods used maximize information and minimize testing time and difficulty so that the workflow of the field analyst is not too cumbersome. The results presented in the previous chapters of this dissertation show that handheld instruments can be used to generate useful data that, if entered into a database, could be retrieved by forensic scientists and members of the law-enforcement community to perform important review and comparisons that may be used to source counterfeit drugs. For these reasons, a proposed

workflow for the analysis of suspected counterfeit tablets to be used in the field is shown in Figure 66.

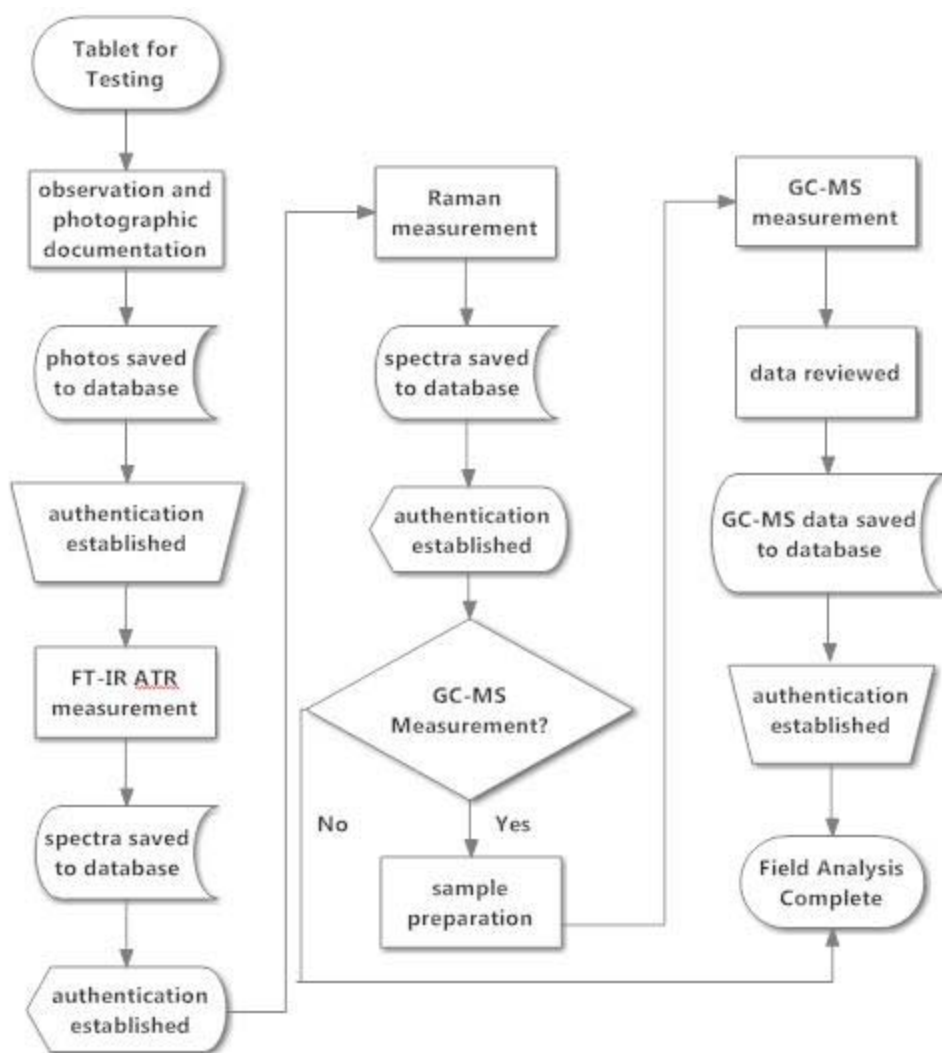


Figure 66. Workflow proposed for testing suspected non-authentic tablets in the field.

It is important to highlight that this scheme is intended for field use by non-scientists, and is not intended to replace lab-based methods that may be used to establish authenticity. The purpose when performing this scheme in the field is to detect differences between the test sample and authentic versions of the sample. While it is true that if differences are detected a sample can be labeled as non-authentic, if no differences are detected, authenticity is not confirmed.

Determination of authenticity is likely best performed in a laboratory setting using methods that are more discriminating. Frequently, conferencing between the brand owner and the forensic scientist will prove to be the best way to determine the best methods to verify authenticity in the laboratory. The brand owner is most familiar with their product and can provide insight as to what methods work best. Figure 67 shows a general workflow for laboratory analysis of methods. It's important to note that depending upon the sample, some methods may be better than others. It is also important to note that this scheme is not inclusive of all potential methods of analysis.

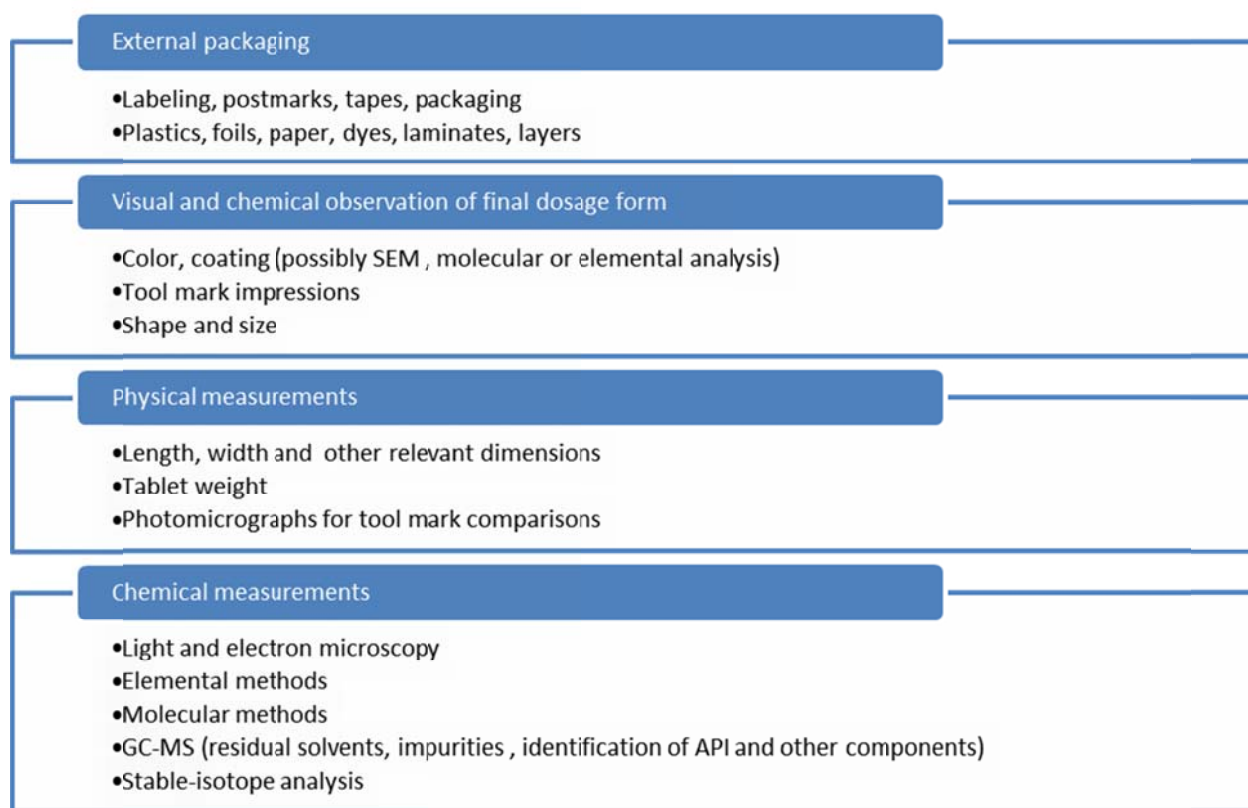


Figure 67. Workflow proposed for lab-based analysis of suspected non-authentic samples.

Analytical Workflow

The first step of any analytical scheme to be performed in the field to test counterfeits is observation and photographic documentation. All photographs should be taken under the same conditions and saved to the database. Review of the data to establish authenticity from a physical examination would likely be manual unless image-analysis methods are developed. For this reason, it may be important to have a second analyst reviewing data in near-real time, especially if a non-authentic sample is detected. This way any conclusions drawn by the field analyst are supported by a second analyst. Tablet color, indicia, and dimensional measurements will frequently enable fast and simple differentiation of authentic from non-authentic samples. The most significant challenge to this type of analysis is that it requires that the analyst have knowledge of the appearance of authentic versions of the drug product. This may or may not be the case. Determination of whether or not a suspect tablet is indistinguishable from the authentic sample is based upon physical appearance, and would be made by the analyst after direct comparison of the physical properties of the sample. Groupings of tablets in the database by the forensic scientist based upon visual appearance may be attempted at a later date if determination of source or origin is desired. Measurements may be taken at the time of inspection, but if no reference is available for comparison, this step is not necessary. Photographs captured at the same magnification can be reviewed at a later time to determine tablet dimensions, if necessary.

The next step in the analytical process is to collect infrared spectra from the tablet using a field portable ATR FT-IR spectrometer. A system that uses a larger analysis spot size is preferred in order to sample the largest amount of sample during collection of a single spectrum. Infrared spectra collected from the tablet's coating and from its core can be automatically searched against electronic databases of library reference spectra to establish a match factor

between the spectrum from the test sample and library spectra of authentic samples. Results are fast, and a numerical value is assigned to establish similarity quantitatively. ATR FT-IR spectra are very reproducible for various reasons. (Reffner & Martoglio, 1995) It would, therefore, be appropriate to assign a minimum match factor score to be used to automatically determine that the suspect tablet cannot be differentiated from authentic versions using this method. If the match-factor value is met or exceeded, the tablet cannot be differentiated from the authentic reference; if the match-factor value is not met, the sample is identified as a non-authentic. The instrument could be programmed to generate a real-time pass/fail result to automatically appear on the instrument's results screen at the time of analysis dependent on the sample's match factor. Infrared spectra collected, regardless of whether or not they are displayed on the instrument's result screen, should be stored in an electronic database. Storage of spectral data in a searchable database would allow forensic scientists and law-enforcement personnel performing investigations to use the data to generate investigative leads. This type of review may be used to group samples together so that provenance may be established.

The next step in the analytical process is to perform a Raman measurement of the tablet core using a portable Raman spectrometer. Just like with infrared spectrometry, a Raman spectrum collected from the tablet's core can be automatically searched against electronic databases of library reference spectra to establish a match factor between the spectrum from the test sample and library spectra of authentic samples. Results are fast, and a numerical value is assigned to establish similarity quantitatively. Although Raman spectra are generally reproducible, differences in peak intensities and other small artifacts of the measurement may be observed between spectra. A minimum match-factor score can be used to automatically determine that the suspect tablet cannot be differentiated from authentic versions using this

method. If the match-factor value is met or exceeded, the tablet cannot be differentiated from the authentic reference; if the match-factor value is not met, the sample is identified as a non-authentic. The instrument could be programmed to generate a real-time pass/fail result to automatically appear on the instrument's results screen at the time of analysis. Raman spectra collected, regardless of whether or not they are displayed on the instrument's result screen, should be stored in an electronic database. Storage of spectral data in a searchable database would allow forensic scientists and law-enforcement personnel performing investigations to use the data to generate investigative leads. This type of review may be used to group samples together so that provenance may be established.

The next and final analytical step in the process is GC-MS analysis to determine a tablet's residual-solvent and organic-volatiles profile. GC-MS is different from the other analytical methods proposed as part of this analytical scheme because it requires sample preparation that is time consuming (approximately 25 minutes). In addition, analysis time is on the order of minutes rather than seconds. The ability to establish this profile is powerful, though, especially in providing investigative information. Solvents and volatile compounds detected and identified may be used as chemical markers. These markers can be used to group samples together and can provide information about manufacturing methods and processes. This information can be very helpful when establishing provenance.

Use of all of these methods has value. Photographs make it possible to easily observe differences amongst samples. Both infrared and Raman methods provide chemical information about the sample and can be used to quickly detect non-authentic samples. Each method (infrared and Raman) has its benefits, and while some information interpreted from the data from these two methods may be redundant, the methods complement each other well and provide a

more complete picture of the nature of the sample. Performing photography, infrared and Raman analysis of a sample may occur in less than five minutes. It is important to recognize that the goal of this field analysis is to detect non-authentic samples. It is not the goal of this analysis to verify authenticity. Using these methods, the inability to detect differences should not be confused with verification of authenticity.

GC-MS analysis is also proposed as part of this scheme because the data can be quite informative and is not redundant to photography, infrared, or Raman analysis. However, the challenges related to time and value to the field analyst should be considered before inclusion of GC-MS in the field-testing scheme is finalized.

Something else to consider is that when using this analytical scheme, the tablet sample rather than the packaging needs to be analyzed. Methods like radio frequency identification tags are useful at tracking and tracing drugs through the supply chain (Rudolf & Bernstein, 2004), but this technology is usually applied to packaging and is not useful in situations where packaging has been removed or repackaging occurs. Alternative methods that require analysis of the sample contained within the packaging are necessary.

Database Management

The methods described as part of this analytical workflow for analysis of samples in the field provide physical and chemical information about samples analyzed. The primary goal, especially for the field analyst, is to detect and identify non-authentic samples. However, data collected can provide much more value if it is stored in a database for retrieval and review by forensic scientists or other law-enforcement personnel. The methods proposed are well suited for analysis in the field. The data is relatively easy to collect quickly. The technologies used allow for interpretation of the physical and chemical nature of the sample. The ability to

maintain this data in a searchable database format is powerful because it enables offline processing and review of large amounts of data from remote and potentially distant locations. This capability is well suited to the challenge of counterfeit drugs. These goods come from different regions of the world, and the place of manufacture is frequently geographically distant from the place of sale or consumption. The ability to collect data from different geographical locations, combine them into a single database, and then review and process to evaluate trends and perform other interpretations is invaluable. There are some anticipated challenges in managing a database of this magnitude. Creation, implementation, and maintenance of the database each offer unique challenges that need to be addressed.

The way in which the database is formatted during its creation is important and, ultimately, will be directly related to its success. The goal is for the forensic scientist to be able to take data from the database and review this data in as simple and straightforward a manner as possible. Therefore, it will be important to be able to search the database using many different search criteria. For instance, in one situation it may be important to search based upon data collection site, or time and date of data collection, while in another the critical search criterion may be the purported drug product. The anticipated use and users should be considered during database creation so that the database is as user friendly as possible. In addition, a method for inclusion into the database of customs documents and other appropriate paperwork should be considered.

Another important factor to consider during database creation is file formats for data storage. It is important that if handheld devices from different instrument manufacturers of the same technology will be contributing to the database, it should be required that files written be converted to a general data format that is not dependent upon which manufacturer's instrument

was used to collect the file. For instance, infrared data could be collected and reviewed in the field using the proprietary software that generates a pass/fail response and then converted to a general infrared data file format like *.spc or *.csv when the file is written to the database. Determination of the best database format for each technology, as well as other data processing requirements should be considered in detail during the creation of the database.

Other items for consideration during creation of the database include networking capabilities and security, speed of internet, availability of internet cabling at anticipated field sites, user interface, and other factors that impact data collection in the field like efficiency and simplicity.

Implementation of a program to analyze and centrally store data from different locations seems complicated, but is manageable. Practically, the field analyst's job may be as simple as collecting data using a handheld instrument, reading off a result and sending the file to the database. Training is important so that useful data is collected. For instance, photographs taken need to be in focus and at a uniform magnification. If not, their value is limited. For spectral files, the spectrum collected needs to be of an appropriate quality so that when compared with data collected from other sites, effective comparisons may be made.

It is also important to manage the amount of data collected and keep the data collection as uniform as possible from site to site. Although it is nice to be able to collect every piece of data and make available to the user every possible option for data processing and review, this would be an overwhelming training burden and would likely not be successful. Handheld cameras and infrared and Raman spectrometers currently available are capable of meeting the field challenges. However, field analysis with GC-MS is more complicated and requires more time for analysis than infrared and Raman measurements. Modifications to workflow in the field

would need to be made to streamline them into the process, specifically considering sample preparation time to generate chemical profiles of residual-solvent and organic-volatile profiles. As previously stated, the use of GC-MS to establish a sample's residual-solvent profile may not be appropriate at high-volume border crossings, but at locations where data collection of this type is possible, inclusion in the database would provide very valuable insight as to the chemical composition of the sample, as well as its method of manufacture. GC-MS files, although complex, can be simplified into a common data format so transfer of the data would be possible.

Maintenance of the database would be required. Aside from maintenance issues related to the server and other hardware, networking and service provider issues need to be addressed. A plan for management of software changes and bug fixes need to be in place. In addition, it would be beneficial to have routine audits of data entered into the database. This would verify that data collected in the field meets minimum quality standards so that meaningful results are possible when data is accessed by the forensic scientists and other users for review.

Admissibility in Court

Forensic scientists are typically considerate of whether or not the testing they perform will be admissible in court. The question of admissibility in court is complicated to answer when considering the testing and workflow provided in this analytical scheme. When considering analytical testing in the field to determine authenticity, the answer to this question is not usually dependent upon the fundamental technology of the instrument, but rather on the methods and procedures in place for use, maintenance, and workflow when using the instrument, as well as on the training and education of the analyst.

The methods used in this research for field analysis of suspected counterfeit drugs using infrared, Raman and GC-MS technologies provide the end user with the ability to distinguish an

authentic from a non-authentic sample. These three technologies have all been successfully admitted in court when tested against the standards for the detection and identification of drugs when used in a laboratory setting. (State of Arizona, Appellee, v. Ronald Michael Lucero, Appellant, 2004; The People of the State of New York, Plaintiff, v. Donald Roraback, Also Known as Donald Reed, Also Known as Tom Reed, Defendant, 1997; Warner Chilcott Laboratories Ireland Limited, et al., Plaintiffs, v. Impax Laboratories, Inc., et al., Defendants. Warner Chilcott Laboratories Ireland Limited, et al., Plaintiffs, v. Mylan Pharmaceuticals Inc., et al., Defendants., 2012) For all three technologies, instrument design and the type of data generated between lab-based and field-portable instruments is consistent. This would lend support for the admissibility of these field-portable technologies in court. However, there are many factors that need to be considered if results collected from a field user were to be admissible in court including maintenance and calibration, instrument performance testing, user training and experience, standards for comparison, and purpose of testing.

Proper maintenance and calibration allows the end user to be confident the instrument is performing in accordance with manufacturer specifications. It is critical that these functions be documented, and that a record of all maintenance performed is available for review. Procedures should be in place to verify that this is the case. Procedures should also be in place to verify that as soon as an instrument fails performance testing, these issues are addressed. It is reasonable to expect that these criteria could be met when deploying these instruments in the field. Infrared, Raman, and GC-MS portable instruments are quite robust, and it is reasonable to assume that when using commercially available instruments, maintenance and calibration requirements in the field would not be too great a burden to meet.

Instrument performance testing is also very important for field-portable instruments. When using infrared and Raman systems, this type of testing is fast and easy and could easily be incorporated into the workflow for these instruments in the field. For GC-MS systems, the methods used to verify performance are a little bit more complicated and may require more time for this aspect of the workflow. This requirement of time would further burden an already time-consuming field method. However, the value of this data collected, as previously described, is high and likely worth the investment of time required in situations where time for analysis is available.

User training and experience is a big factor impacting admissibility of scientific evidence because users of the technology may not have a strong background in a scientific discipline. Typically, end users are not scientists, but are expected to be able to interpret scientific evidence. Field-portable instruments are intended to be easy to use and designed to generate results rather than data. In fact, most field users rely on the match factor generated by the handheld instrument rather than concern themselves with interpreting a spectrum. However, extensive training on the theory and design of the technology and the instrument or on the process used to generate match factors is not usually extensive. Therefore, the field analyst is not acting as a scientist in their approach to the evidence, but rather as a technician. This does not mean that the evidence is inherently inadmissible (*Kumho Tire Company, Ltd., et al., Petitioners v. Patrick Carmichael, etc., et al.*, 1999). However, it does present challenges in court when considering the individual who performs the test and his or her suitability to testify in court. It would be prudent to establish procedures that verify that the person determining that a sample is non-authentic understands how the instrument works, what aspects of the sample are being tested, what the data means, and other things an expert witness should understand about the method and

technology. There are ways to address this. For instance, a scientist could be assigned to supervise all non-authentication determinations. This person could be responsible to review the data in real time and verify the data and results used to determine authenticity are accurate. Field-portable instruments and the workflow described in this dissertation are not used to verify authenticity, but rather to detect non-authentic samples. The supervisory scientist could represent the data when presented in court.

It is not reasonable to expect that standards for comparison would be available for testing during field analysis, or that time would be available in the field to perform such testing. When performing analysis in the field, end users are forced to rely on electronic libraries of data available on the handheld unit. This is not necessarily a problem because the quality of the library used can be secured and verified prior to deployment of the instrument. However, it is typical for an analyst working in the lab to not make analysis determinations based upon a library-search result, but rather to use these electronic databases to identify unknowns. The lab analyst identifies an unknown by comparison with a library spectrum. They then will typically prepare a standard of the unknown and analyze the sample using the same methods they use to analyze the unknown sample for direct comparison of the standard with their unknown, and to evaluate whether or standard spectrum is incongruous with the unknown spectrum. This paradigm would likely extend to field applications and would be a problem for admissibility of field-testing results. It is important that these points be considered if results for field tests are to be admissible in court.

One of the most important items to consider when determining whether data from field-portable instruments is admissible in court is the purpose of the field test. In this analytical scheme presented, data collected in the field would be used to demonstrate that a sample is not

authentic. It is reasonable to expect that infrared, Raman, and GC-MS methods would all be capable of performing this function effectively. However, it is important that the analyst understands the value and the limitations of the instrument, the technology, and the test. It is also important that the testing be performed accurately, and in accordance with established methods and procedures.

When meeting the standards for admissibility of evidence in court in the United States, it is likely, as previously referenced, that field-portable infrared, Raman, and GC-MS methods would meet the standards for admissibility. However, challenges to admissibility would be faced based upon the systems and procedures in place to describe the workflow, the standards used for comparison, and the training and experience of the analyst. These points are important to consider, but it is reasonable to expect that when these issues are considered and addressed, court-admissible field tests for the detection of non-authentic samples is possible.

Summary

Analysis of pharmaceutical tablets using this analytical scheme would enable the field analyst to identify non-authentic samples rapidly and reliably. The availability of this data collected in the field in a searchable database format would be very valuable to forensic scientists. A significant challenge to forensic science is the determination of source or origin of these illicit goods. It seems that any attempt at sourcing requires access to data from many different samples in order to identify patterns in the samples and the data to ultimately link non-authentic samples to each other. Collection of such data is time consuming and challenging for various reasons. Data compiled from field analysis using appropriate methods as detailed in this dissertation would be very beneficial. This research shows the methods proposed in this analytical scheme for testing in the field may be used to determine source or origin of non-

authentic samples. An accessible database would enable forensic scientists to apply these methods to large numbers of samples and generate meaningful investigative information about the source and origin of non-authentic samples.

CHAPTER 12. PHARMACEUTICAL DEVELOPMENT IN THE UNITED STATES

Drug development in the United States is regulated by the United States FDA. The mission of FDA's Center for Drug Evaluation and Research (CDER) is to ensure that drugs marketed in the United States are safe and effective. (Food and Drug Administration, 2014) Although the mission of CDER is safety, it is important to recognize that drug development (as regulated by FDA) is inseparably intertwined with the patenting system and protection of IP rights. Pharmaceutical innovation and the patenting of new drugs and inventions are part of the business strategy of pharmaceutical development (Thakur & Ramacha, 2012), and mechanisms are in place throughout the regulated drug-development life cycle to allow IP owners to protect their inventions.

Patent protection is the primary incentive to pharmaceutical innovators to develop new medicines. Patent protection ensures market exclusivity for a specified period of time. This market exclusivity is guaranteed under FDA regulation for drugs sold in the United States upon FDA approval. This period of market exclusivity is when most of the financial investment in development is recouped. (Melethil, 2005) For instance, Lipitor® total sales were well over \$100 billion before its patent expired. (Phelps, 2012) Failure to protect IP rights by allowing the infiltration of counterfeit and substandard drugs that violate IP rights threatens the future of pharmaceutical innovation because it minimizes the incentives to invest in the development of new drugs. In terms of profitability, backing blockbuster drugs over many decades made big pharma what it is today, but as time goes on, it has become evident that the risks of this strategy are increasing and the rewards decreasing. (Phelps, 2012) Lack of incentive to innovate could have devastating consequences on public health because new drugs are needed to address the continually changing needs of public health. A review of some of the aspects of FDA regulation

of the drug-development process, especially related to the granting and protection of IP rights, is presented for consideration.

Drug Applications

Approval to sell pharmaceuticals in the United States is usually granted through one of a few types of applications. The first is a new drug application (NDA); the second is an abbreviated new drug application (ANDA). Pharmaceutical innovators that bring a new drug to the market will typically submit their request for approval using an NDA. Generic manufacturers requesting approval to market generic versions of approved drugs will submit their request for approval using an ANDA. A third type of application, sometimes referred to as a section 505(b)(2) application, is different from both the NDA and ANDA. This type of application has significant IP considerations. Section 505(b)(2) applications are specific for applications that contains full reports of investigations of safety and effectiveness, but where at least some of the information required for approval comes from studies not conducted by or for the applicant, and for which the applicant has not obtained a right of reference (IP claim). In comparison, NDA filings contain full reports of investigations of safety and effectiveness conducted by or for the applicant; ANDA filings do not contain full reports of investigations of safety and effectiveness, but rather contain information to show that the proposed product is, among other things, identical to a previously approved product in active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics, and intended use. The requirements for these three different applications are dramatically different and are briefly reviewed.

New Drug Application

The NDA is the formal step a drug sponsor takes to ask that the FDA consider approving a new drug for marketing in the United States. An NDA includes all animal and human data and analyses of the data, as well as information about how the drug is manufactured and behaves in the body. Once an NDA is received by FDA, the FDA has 60 days to decide whether to file it so that it can be reviewed. The FDA can refuse to file an application that is incomplete. For example, some required studies may be missing. (Food and Drug Administration, 2014)

Once an NDA is filed, an FDA review team of medical doctors, chemists, statisticians, microbiologists, pharmacologists, and other experts evaluate whether the studies the sponsor submitted show that the drug is safe and effective for its proposed use. "Safe" in this sense means that the benefits of the drug appear to outweigh the known risks. The review team analyzes study results and looks for possible issues with the application such as weaknesses of the study design or analyses. Reviewers determine whether they agree with the sponsor's results and conclusions, or whether they need any additional information to make a decision. Approval to market is granted after the NDA and labeling are approved, and facility inspections are completed. (Food and Drug Administration, 2014)

Although the NDA is the formal request a drug sponsor makes to FDA for approval to market a drug in the United States, the process of drug development and the sponsors interactions with FDA begin years before an NDA is filed. Initially, researchers work to either synthesize or identify new drugs viable for development. Many drugs may be synthesized, but only a small number are deemed viable for testing in animals. Most drugs that undergo testing in animals never make it to human testing and review by the FDA. Further to this, hundreds more fail in clinical trials. (Phelps, 2012)

Permission to test drugs in humans (which is a required step before submitting an NDA) is only granted after an investigational new drug (IND) application has received FDA approval. Drug sponsors submit an IND to the FDA to request permission to test the drug in humans. During the IND approval process, the FDA scrutinizes everything about the drug from the design of clinical trials, to the severity of side effects, to the conditions under which the drug is manufactured. Sponsors, which may be companies, research institutions, or other organizations taking responsibility for developing a drug, must show the FDA results of preclinical testing in laboratory animals, as well as what they propose to do for clinical testing. At this stage, the FDA decides whether it is reasonably safe for the drug sponsor to move forward with clinical testing.

Once an IND application is approved, the drug sponsor spends years in development to pass through the various phases of clinical trials to ultimately submit an NDA. Clinical trials can begin only after an IND is reviewed by the FDA and a local institutional review board (IRB). The board is a panel of scientists and non-scientists in hospitals and research institutions that oversee clinical research. IRB's approve the clinical-trial protocols, which describe the type of people who may participate in the clinical trial, the schedule of tests and procedures, the medications and dosages to be studied, the length of the study, the study's objectives, and other details. IRB's make sure the study is acceptable, that participants have given consent and are fully informed of their risks, and that researchers take appropriate steps to protect patients from harm.

The process of NDA approval is time consuming and expensive. DiMasi and colleagues estimated average out-of-pocket direct cost per new drug is \$403 million United States dollars (2000 dollars). Capitalizing out-of-pocket costs to the point of marketing approval at a real discount rate of 11% yielded a total pre-approval cost estimate of \$802 million United States

dollars (2000 dollars). (DiMasi, Hansen, & Grabowski, 2003) There are some that have argued these cost estimates, but most agree that the cost to develop new drugs is in the hundreds of millions of dollars, but can be quite variable. Variability in cost estimates depends upon many factors including the type of drug developed. In addition to the high costs, the process of new drug approval is long and complicated. Figure 68 summarizes the drug-development process for drugs approved through the NDA process.

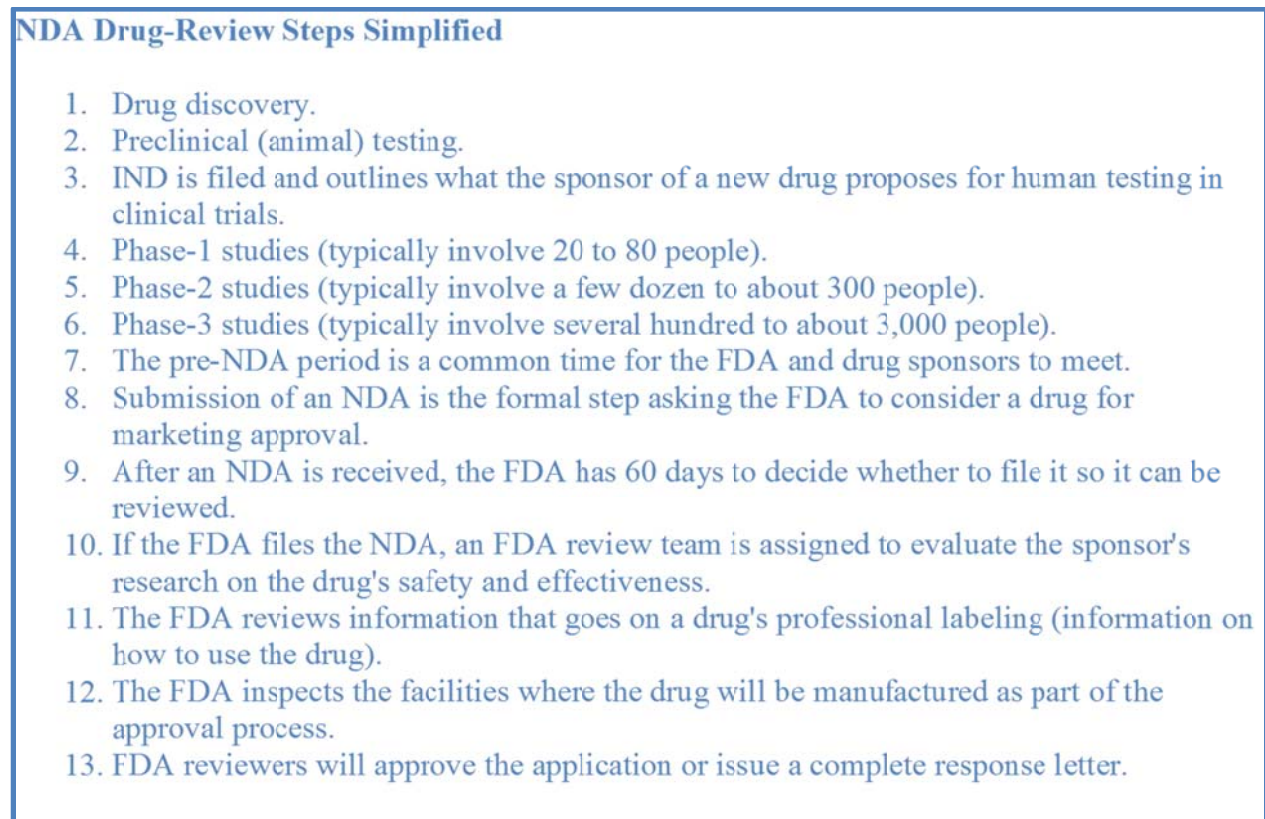


Figure 68. Summary of the drug-development process for drugs approved for innovative drugs.

Ultimately, the result of a successful NDA filing for the drug sponsor is a new or innovative drug for sale in the United States. Some of these drugs have been shown to control or even eradicate sickness and disease. (International Task Force for Disease Eradication, 1993)

The role these drugs play in developed societies is critical.

Abbreviated New Drug Application

An ANDA contains data which, when submitted to FDA's CDER, Office of Generic Drugs (OGD), provides for the review and ultimate approval of a generic drug product. The OGD is responsible for providing regulatory oversight to expedite the availability of safe, effective, high-quality generic drugs to patients. The OGD also provides guidance to the regulated industry on a wide variety of clinical, scientific, and regulatory matters relating to generic drugs. Part of the mission of the OGD is to maintain the public's confidence in an FDA as it continues to meet the ever-changing needs of public health.

Once an ANDA is approved, an applicant may manufacture and market the generic drug product in the United States to provide a safe, effective, low-cost alternative to the American public. A generic drug product is defined as one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use.

Generic drug applications are termed "abbreviated" because drug sponsors are generally not required to include animal and human data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the innovator drug). One way scientists demonstrate bioequivalence is to measure the time it takes the generic drug to reach the bloodstream in 24 to 36 healthy volunteers. This gives them the rate of absorption, or bioavailability, of the generic drug, which they can then compare to that of the innovator drug. The generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the innovator drug. ANDA reviewers focus on bioequivalence data, chemistry and microbiology data, requests for plant inspection, and drug labeling information.

The costs to bring generic drugs to the market are significantly lower than they are for new drugs. A primary reason for this is because many of the expensive and risky aspects required of an NDA filing are not a factor when seeking approval to market generics. Drug discovery and proof of safety and efficacy are major components of the NDA life cycle that are risky and expensive. They are not required steps for a generic drug sponsor. In addition, much of the marketing and advertising costs for generics are lower than they are for new drugs. (Food and Drug Administration, 2014)

505(b)(2) Application

A 505(b)(2) application may be submitted for a new chemical entity (NCE) when some part of the data necessary for approval is derived from studies not conducted by or for the applicant and to which the applicant has not obtained a right of reference. For an NCE, this data is likely to be derived from published studies, rather than FDA's previous finding of safety and effectiveness of a drug. It is important to note that if the applicant had a right of reference to all of the information necessary for approval, even if the applicant had not conducted the studies, the application would be a considered an NDA.

A 505(b)(2) application may also be submitted for applications based upon changes to a previously approved drug product. The application may rely on FDA's finding of safety and effectiveness of the previously approved product, coupled with the information needed to support the change from the approved product. The additional information could be new studies conducted by the applicant or published data. This use of section 505(b)(2), described in the regulations at 21 CFR 314.54, was intended to encourage innovation without creating duplicate work and reflects the same principle as the ANDA, i.e., it is wasteful and unnecessary to carry out studies to demonstrate what is already known about a drug.

An applicant should file a 505(b)(2) application if it is seeking approval of a change to an approved drug that would not be permitted using an ANDA, because approval will require the review of clinical data. However, section 505(b)(2) applications should not be submitted for duplicates of approved products that are eligible for approval using an ANDA. In addition, an applicant may submit a 505(b)(2) application for a change in a drug product that is eligible for consideration pursuant to a suitability petition under Section 505(j)(2)(c) of the Act.

Although a 505(b)(2) applications is not applicable to all drug applications, there are situations when this option is useful. Some examples include (1) applications for pediatric drugs where results of studies performed on adults may be extrapolated to apply to pediatric patients, (2) instances of bioequivalence where alternative formulations and new dosage strengths may be assessed on the basis of evidence of bioequivalence, instances where modified release dosage forms may be approved on the basis of pharmacokinetic data linking the new dosage form to an approved immediate-release dosage form, and (3) in situations of different doses, regimens, or dosage forms where blood levels and exposure are not very different. In these instances, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data alone.

Drug Development and Patent Protection

The research and development required to gain approval to market a drug in the United States is dramatically different depending upon whether the drug is innovative or generic. Regardless of which application and subsequent development process is followed, however, FDA regulation holds the value of IP rights to be fundamental. Mechanisms for protection of these rights through enforcement and legal action are integrated throughout all application processes.

Pharmaceutical innovators seeking approval to market drugs in the United States using the NDA typically are performing development for drugs they've either patented or licensed from a patent holder. Patents are granted and protected for a specified amount of time. FDA regulations require drugs be approved before they are sold in the United States. Therefore, the earlier in the development process the inventions are patented, the shorter the amount of market exclusivity time (because the longer the patented invention will be in the approval process.) Loss of market-exclusivity time due to time spent gaining approval to market is an inherent consideration of the drug-development process in the United States. The Hatch-Waxman Act addresses these details and will be considered in chapter 14. At this point, though, it is important to understand that it is typical that drugs approved through the NDA process are patented, and patenting strategies attempt to reconcile time lost in development with protection of market-exclusivity time.

The approach to patents and IP rights when seeking approval to market generic drugs using the ANDA process is extremely different than it is for the NDA process. As part of the ANDA process, generic manufacturers attempt to demonstrate bioequivalence of innovative drugs that are patent protected so that these patented inventions become available to the public on the date the patent expires. Using bioequivalence as the basis for approving generic copies of drug products was established as part of the Hatch-Waxman Act. Typically, it is not legal to practice patented inventions until after patents expire. In the case of pharmaceutical patents, this is not the case. Giving generic drug sponsors rights to practice patented inventions are also an inherent consideration of the Hatch-Waxman Act. Fundamentally, though, generic drug sponsors are required to adhere to laws governing patented inventions. The ANDA process requires that patent holders are advised of potential infringements of their inventions.

To begin the FDA approval process, the generic applicant must: 1) certify in its ANDA that the patent in question is invalid or is not infringed by the generic product (known as "paragraph IV certification"); and 2) notify the patent holder of the submission of the ANDA. If the patent holder files an infringement suit against the generic applicant within 45 days of the ANDA notification, FDA approval to market the generic drug is automatically postponed for 30 months, unless, before that time, the patent expires or is judged to be invalid or not infringed. This 30-month postponement allows the patent holder time to assert its patent rights in court before a generic competitor is permitted to enter.

Patents and IP rights are also integrated with section 505(b)(2) applications. The filing or approval of a 505(b)(2) application may be delayed due to patent or exclusivity protections covering an approved product. Section 505(b)(2) applications must include patent certifications described at 21 CFR 314.50(i) and must provide notice of certain patent certifications to the NDA holder and patent owner under 21 CFR 314.52. The certifications are required and force the 505(b)(2) applicant to directly address their impact on the IP of others.

The drug-development process in the United States is complicated, but it is important to recognize the value placed upon IP rights and their protection during this process. These rights are fundamental in developed societies, and violation of them when considering pharmaceutical innovation is a significant threat to public health. Sale of counterfeit drugs violates these IP rights. Sale of drugs in the United States without FDA approval is illegal and poses a significant threat to public health. Marketing of substandard drugs throughout the world undermines the system in place in the United States for pharmaceutical innovation and poses long-term threats to public health.

CHAPTER 13. PATENTS AND SOCIETY

As described in chapter 12, IP and IP-rights protection are fully integrated in the process of gaining approval to market a drug for sale in the United States, regardless of which application route the drug sponsor pursues. This type of integration demonstrates the value developed societies like the United States place upon IP. IP fosters innovation and promotes society. The patenting system is an important part of the drug-development process. A brief review of patenting in the United States and patenting related to drug applications to FDA is considered.

The first issued patent in the American colonies was granted in 1641. The first United States patent was granted in 1790. A patent in the United States is an IP right granted by the government of the United States to an inventor “to exclude others from making, using, offering for sale, or selling the invention throughout the United States, or importing the invention into the United States” for a limited time in exchange for public disclosure of the invention when the patent is granted. (The United States Patent and Trademark Office, 2014)

Patents are granted to inventions that are novel and nonobvious. They are a trade between society and the invention owner that provides benefit to both parties. The inventor benefits because they enjoy market exclusivity for a specified period of time. This market exclusivity provides financial incentive to the IP owner, and may be considered reward for the contribution their invention will make to society. In the pharmaceutical industry, the potential to recoup the initial investment required to develop the invention during this time of market exclusivity is a significant incentive. This is because the process to achieve FDA approval to sell a pharmaceutical in the United States is long, risky, and expensive. Society benefits from the

patented invention because details of the best practice of the invention are available for all members of society to use upon patent-term expiration.

Disclosure and details of the best practice of the invention is required as part of the patenting process. However, even though the details of the invention are available for review at the time the patent is granted, patent law forbids the practice of the invention until the patent term expires. This is fundamental to patent law in the United States, and the concept dates back in patent history as far as 1474 to the Venetian Senate Act.

The Venetian Act lays out all the essential features of a modern patent statute including an established procedure to determine infringement, as well as a remedy for infringement. It covers “devices”; states that they must be registered with a specific administrative agency; it says that they must be “new and useful”, “reduced to perfection”, and “not previously made in this Commonwealth”. The Venetian Act also provides a fixed patent term of ten years. Interestingly, the Venetian Act reserved to the Republic the right to use any invention without compensating the inventor. This is an early attempt to reconcile individual interest with the good of the community. It implies that the inventor’s protection, provided by the grace of the state, ought naturally to be subject to the needs of the state. (Merger, 1997)

Patents, patent terms, and patent law for drug-related and medical-device inventions in the United States are different than they are for all other types of patents. The reason for this difference is because society in the United States recognizes the balance between pharmaceutical innovation and providing access to affordable medication. To account for this balance, pharmaceutically relevant patents allow for time spent gaining FDA approval. Patent law for pharmaceutically relevant patents also allow for legal infringement of patented inventions when the purpose of such infringement is to provide generic alternatives upon patent-term expiration.

These differences in patent law are a result of the Hatch-Waxman Act. Patent terms and legal infringement of patent inventions related to the pharmaceutical industry are described in this chapter. The impact of the Hatch-Waxman Act will be discussed in chapter 14.

Patent Terms

Normally, patent terms are for 20 years. It is expected that for a normal patent, the patent-application process may take up to three years. Since the patent term begins on the initial date of the patent application, the effective term of a normal patent for market exclusivity is usually about 17 years. (Pensabene & Gregory, 2013) Prior to the Hatch-Waxman Act, patent terms were the same in the drug-development world, but the effective time for market exclusivity was usually shorter due to the inability of the patent owner to market until FDA approval. Gaining this approval would usually take years. Patents for inventions related to drug development now compensate for market exclusivity time lost gaining regulatory approval. Patent-term extension is provided for patents covering certain products and methods, including human drug products, that are subject to FDA approval. (35 U.S.C. § 156; *Eli Lilly and Company, Petition v. Medtronic, Inc.*, 1990) The patent's term can be extended by a maximum of five years or 14 years of effective patent life, whichever is less. Specifically, the patentee is entitled to a credit for the time the FDA was reviewing the first drug application. (Pensabene & Gregory, 2013)

Legal Infringement

To balance the extension in patent term for pharmaceutically relevant compounds, practice of the patented invention is allowed in some circumstances. Specifically, practice of the invention is allowed when the goal of the practice is to develop a generic alternative that can be provided to the consumer on the date of patent-term expiration. Prior to this change in the patent

system, generic manufacturers were required to wait until patent-term expiration before they could begin the process of developing generic alternatives. This led to an effective extension of market exclusivity prior to the Hatch-Waxman Act and, therefore, generic (more affordable) alternatives took longer to reach the public.

It is clear the benefit to society of pharmaceutical innovation resulting from IP protection cannot be overlooked. Innovative drugs have eradicated many diseases and improved quality-of-life standards throughout the world. (International Task Force for Disease Eradication, 1993)

The patenting system is an integral part of the drug-development process. This system promotes pharmaceutical innovation and offers long-term benefits to society.

CHAPTER 14. THE DRUG PRICE COMPETITION AND PATENT TERM RESTORATION ACT OF 1984

The patenting of pharmaceuticals in the United States went through a significant change as a result of the Hatch-Waxman Act. This Act establishes certain rights and procedures in situations where a company seeks FDA approval to market a generic product prior to the expiration of a patent or patents relating to a brand-name drug upon which the generic is based. Congress enacted this law to facilitate the entry of lower-priced generic drugs, while maintaining incentives for pharmaceutical companies to invest in developing new drugs.

There were two related issues that were addressed by the Hatch-Waxman Act. First, when new drugs were discovered and patents applied for, the patent was issued before the FDA regulatory approval process for the new drug was complete. Thus, the patent term would begin to run, but the patent owner could not market the product until the FDA approval process was completed. As a result, patent owners seeking FDA approval would lose time in market exclusivity due to regulatory requirements. Second, generic drugs could not begin development until patent terms expired. Under *Roche v. Bolar* (*Roche Products, Inc. Appellant, v. Bolar Pharmaceutical Co., Inc., Appellee*, 1984), the testing of a generic equivalent to a patented drug for the purpose of obtaining the FDA's approval was deemed infringement. Accordingly, a competitor hoping to produce a generic product had to wait until the patent expired before it could begin the often-lengthy process of obtaining FDA approval. Thus, from the time the patent expired until a competitor obtained FDA approval, the patent owner enjoyed an effective extension of market exclusivity. The Hatch-Waxman Act reconciled these two related issues and fundamentally changed the patenting system in the United States.

With regard to the first issue, patent terms under the Hatch-Waxman Act for pharmaceutically relevant inventions were extended. Most United States patents have a 20-year

term measured from the original application's filing date. Since the application process for most patents (non-drug) typically takes about three years, a patent's effective life is usually about 17 years from its issuance. This term is subject to patent-term adjustment for USPTO delays during patent prosecution that shrink the effective life below 17 years. (35 U.S.C. § 154(b))

Virtually all drugs approved through the NDA process are covered by one or more patents. The effective patent term for patents covering a new drug is typically much shorter than 17 years because the time-consuming FDA approval process typically occurs during part of the patent term. As a result, branded drug companies do not enjoy the full benefit of the patent until the FDA approves the drug and sales can begin. (Pensabene & Gregory, 2013) As a partial remedy, the Hatch-Waxman Act provides a patent-term extension for patents covering certain products and methods, including human drug products, which are subject to FDA approval. (35 U.S.C. § 156; *Eli Lilly and Company, Petitioner v. Medtronic, Inc.*, 1990) The patent's term can be extended by a maximum of five or 14 years of effective patent life, whichever is less. Specifically, the patentee is entitled to a credit for the time the FDA was reviewing the first drug application. (35 U.S.C. § 156(a) and 35 U.S.C. § 156(f)(1)(A) and (2)(A))

With regard to the second issue, the Hatch-Waxman Act allowed provisions to benefit generic drug sponsors. The first provision was that the generic drug sponsor did not have to file an NDA to be granted approval to market the generic drug; they could file an ANDA. The importance of this was that requirements for an ANDA filing were different than for the NDA filing, and it was expected that the approval time and cost to gain approval via the ANDA process would be significantly less. Under an ANDA, a generic drug company must establish that the generic drug is effectively a duplicate of the branded, NDA drug, which is referred to as the Reference Listed Drug (RLD). Generic manufacturers were no longer required to perform

clinical testing to prove safety and efficacy. Specifically, the generic drug company must show that the proposed generic drug:

1. Has the same active ingredient, route of administration, dosage form, strength, and intended use as the RLD. It also must have the same labelling, except that the generic drug company sometimes may remove information related to a patented method or use subject to exclusivity from its label. However, the generic drug is not required to have the same inactive ingredients as the RLD (21 U.S.C. § 355(j)(2)(A)).

2. Is bioequivalent with the RLD so that it performs in the same manner as the RLD in the body. Generally, a drug is bioequivalent when it delivers the same amount of active ingredient in a patient's bloodstream over the same amount of time as the RLD. Different but analogous rules apply to drugs that are not delivered in the bloodstream, for example, by topical application (21 U.S.C. § 355(j)(8)).

Additionally, the generic manufacturer must file a certification regarding patents listed in the Orange Book (also known as Approved Drug Products with Therapeutic Equivalence Evaluations). A Paragraph-IV Certification states that the patent is invalid or will not be infringed and begins a process by which that question may be answered by the courts prior to expiration of the patent. Under the Hatch-Waxman Act, FDA approval of an ANDA is automatically stayed for 30 months when a patent owner files a patent infringement lawsuit within 45 days of receiving a Paragraph-IV notification. During the stay, the FDA is prohibited from approving another ANDA. Additionally, the first ANDA is granted a 180-day exclusivity period, as an incentive whereby the generic company does not have competition from other generic companies and can both establish market share and charge a higher price. This higher

price is quite an incentive because the prices charged are usually only slightly below the branded drug and are a time of high profit for the generic manufacturer.

The second provision of the Hatch-Waxman Act to the benefit of generic manufacturers is with regard to practice of a patented invention. Typically, the patented invention may not be practiced until patent-term expiration. In these cases, though, the Hatch-Waxman Act allows generic drug sponsors to practice the invention if the intention is to bring a generic drug to the market. What this practically means is that the generic manufacturer no longer has to wait until patent-term expiration to begin their development and, therefore, could be ready to market their generic product on the date of patent-term expiration. It is important to recognize that this privilege that is extended to generic drug sponsors to legally infringe unexpired patents is unique to specific types of patents.

There are other details of the Hatch-Waxman Act that are important and have changed the business of pharmaceutical development. It is clear that the intention of the Act was to balance pharmaceutical innovation with access to affordable medication. There have, however, been many unexpected consequences. For instance, especially in more recent years, there have been more patent applications by generic companies and increased generic research and development for branded products. Although clearly not a goal of Hatch-Waxman, generics innovate, often obtaining “design-around” patents or a more efficient manufacturing process, new formulations, or new forms of the API. (Rumore, 2009) Conversely, although there are more ANDAs filed than ever, there are an increased number of “me-too” ANDAs and ANDAs for products which already have a generic version. (Silver, 2007)

Although the net effect of Hatch-Waxman on pharmaceutical innovation is ambiguous, its effect on generic drug development has been explicit, and the effect on consumers has been

beneficial. It will be argued in later chapters that the long-term benefits to the consumer are not as clearly beneficial. One thing is for sure. The Act has instigated a flurry of litigation this is costly. The Hatch-Waxman Act resulted in increased ANDA applications and Paragraph-IV challenges, especially since 1998. There has also been a high success rate for patent invalidation, particularly formulation and polymorph patents. Since the Hatch-Waxman Act, virtually all top-selling drugs not covered by patent face generic competition; whereas pre-Hatch-Waxman, only 35% had generics available. Similarly, today more than 70% of prescriptions are for generics, whereas prior to the Act generic prescriptions numbered 15%. (Rumore, 2009) In addition to substantial generic penetration, Saha and colleagues also reported on the generic-to-brand price ratio. Their analysis indicated that the average generic-to-brand price ratio for the drugs in their sample set falls continuously following generic entry. Furthermore, as the entry rate slows down after the first year, so does the decline in the price ratio. A month after the first generic entry, the average price of generics for all 40 drugs evaluated was 76% of the brand price; by the end of the first year it was 54%; by the end of the second year it was 41%. (Saha, Grabowski, Birnbaum, Greenberg, & Bizan, 2006) Under the Hatch- Waxman Act, the average length of patent extension is three years. Overall, there have been some reduced returns on new drugs, but product life cycles have not changed significantly. (Rumore, 2009)

The impact of the Hatch-Waxman Act upon pharmaceutical development has been significant. Not only was the drug-development process impacted, but also the fundamental rights of IP owners were changed to accommodate the balance between innovation and accessibility of the public to needed drugs. There is no question it has increased the availability of generic drugs to that market. Whether it will continue to foster innovation is still to be seen.

CHAPTER 15. ENFORCEMENT OF INTELLECTUAL PROPERTY RIGHTS

Enforcement of IP rights in the pharmaceutical industry, especially as related to the availability of counterfeit, substandard and illegal-imitation drugs, is an important issue that is complex. Even in the United States enforcement can be challenging. In other regions of the world where societies are less developed and IP is not valued, enforcement can be daunting. It seems appropriate, therefore, to discuss the challenges of enforcement in developed societies like the United States separate from enforcement in underdeveloped societies.

Enforcement of Intellectual Property Rights in the United States

In the United States, IP rights are granted and infringement criteria are established. This is especially true during drug development and approval where patent litigation amongst innovative and generic drug companies is common. In addition, the United States has a highly regulated drug-supply chain which minimizes the introduction of counterfeit and other illegal pharmaceuticals into the legitimate marketplace. Finally, the functional legal system of the United States provides a mechanism to enforce instances of IP-rights violation. This is not to say they are always enforced; just that the framework within which they can be enforced is established.

FDA and other regulations make it very difficult, although not impossible, for counterfeit and other illegal pharmaceuticals to infiltrate the legitimate supply chain within the United States. It is reasonable for a consumer in the United States to expect that, assuming they purchase within authorized pharmacies, the pharmaceuticals they receive are what they are purported to be. This is not to say that counterfeit and other illegal pharmaceuticals are not available in the United States, but rather that within the regulated supply chain, they are not encountered with great frequency.

The internet in recent years has made it significantly easier for the American consumer to encounter counterfeit and substandard drugs. Unregulated website pharmacies have added a new dimension to the trade of these goods. Online purchasing has become more common in the United States. However, not all people understand that purchasing medication online is different from purchasing other consumer goods online. Online purchases of pharmaceuticals are very risky, especially if the consumer is unaware of what to look for to detect fraud or other illegal activities when making these purchases. Purchases of pharmaceuticals online may result in the receipt of drugs that are counterfeit, the wrong dose, not approved by FDA, not stored properly during shipment, may contain unsafe ingredients, or have expired. (AWARxE Consumer Protection Program, 2014)

During drug development, the Hatch-Waxman Act works reasonably well to enforce IP rights. The primary legal actions taken during this time include litigation triggered by a Paragraph-IV Certification, where a patent holder believes their patent rights have been violated by an ANDA filing. The patent holder has the right to file a patent infringement suit against the generic applicant and, essentially, will halt the approval of the ANDA for a period of at least 30 months. This 30-month stay allows time for the patent-infringement claims to be reviewed in a court of law. This mechanism for enforcement is quite powerful, and enforcement of patent protection in these cases is possible.

For the patentee, the primary reward for winning a Hatch-Waxman Act patent litigation is continued enjoyment of any unexpired exclusivity. The typical remedies for a prevailing patentee include (1) an order directing the FDA not to approve the ANDA before the expiration of the relevant patents and any other exclusivity, or (2) an injunction against future infringement. Money damages also may be available if the ANDA filer made actual sales. (Pensabene &

Gregory, 2013) In exceptional cases, attorney fees also are available to a prevailing patentee. (35 U.S.C. § 271(e)(4))

For a generic drug company, the primary reward for victory is the ability to enter the market before patent expiration without patent-infringement liability. A prevailing generic drug company that has tentative approval usually can immediately gain final approval and enter the market. If not, the prevailing generic drug company can enter the market once any other exclusivity has expired. This is typically the 180 days of exclusivity held by a first filer. A prevailing generic drug company also may obtain attorney fees in an exceptional case. (Pensabene & Gregory, 2013)

There are some reported abuses of the Hatch-Waxman Act and loopholes that have made for some interesting legal actions. Some of these loopholes have been closed. One such example of a closed loophole is with regard to the 30-month-stay provision related to Paragraph-IV Certification. Once pharmaceutical companies began to realize the advantageous nature of the 30-month stays, they also began looking for ways to extend them beyond the 30-month period. (Eurek, 2003) According to a study conducted by the Federal Trade Commission (FTC) in 2002, one of the most common ways that patent-holding companies were able to further delay the market entry of generic drugs was through multiple patent listings in the Orange Book, which is the FDA's official list of all approved products. The FTC study identified several instances in which brand-name companies listed patents in the Orange Book after an ANDA had already been filed by a generic manufacturer. The effect of these later listings is that the generic applicant was then required to recertify that the later-listed patent is also invalid or not infringed, and notify the patent holder of the recertification. In essence, the generic applicant was required to repeat the ANDA process for the later-listed patent. It was estimated that abuses of this kind

resulted in billions of dollars in additional sales to the patent holders. (Federal Trade Commission, 2002)

The Hatch-Waxman Act was amended several times to close this and other loopholes, as well as to decrease generic drug approval times. (Medicare Prescription Drug, Improvement, and Modernization Act, 2003) Additionally, over the years, the FDA issued many guidance documents clarifying the Hatch-Waxman Act with the goals of reducing generic approval time, improving ANDA application quality to avoid multiple review cycles, and avoiding time-consuming legal delays which delayed competition. (Rumore, 2009)

There are still many legal strategies that are used by brand owners and generic sponsors to gain or maintain market exclusivity. One such strategy is the “at-risk” product launch by generic companies. This strategy involves launching the generic product prior to a district court decision and injunction. In *Sanofi- Synthelabo and Bristol-Myers Squibb v. Apotex* (Sanofi-Synthelabo, Inc.; and Bristol-Myers Squibb Sanofi Pharmaceuticals Holding Partnership, Plaintiffs, -against- Apotex Inc.; and Apotex Corp., Defendants, 2006), three months prior to the FDA’s approving the ANDA, the generic company notified Sanofi that it would launch the generic Plavix® product “at risk.” The generic was launched stocking pharmacy shelves over the course of approximately three weeks, while Sanofi filed for a preliminary injunction. Three weeks later, an injunction was granted with Apotex being “at risk” that it would lose some of the 180-day exclusivity period and the market share associated with it. Even though the court ruled in favor of Sanofi, it denied Sanofi’s request to recall the product that had already been distributed prior to the injunction. During the three-week distribution that occurred as a result of the at-risk launch, Apotex supplied enough of the generic drug pharmacy’s to maintain

domination over Plavix for five months. Apotex received hundreds of millions of dollars in revenue for this at-risk launch. (Pechersky, 2007)

In spite of this and other “legal strategies” that have changed the business of drug development in the United States as a result of the Hatch-Waxman Act, it is important to recognize that this law is intended to balance innovation with access to affordable medicines. Fundamentally, the United States legal and regulatory system affords patent owners with the tools they need to enforce IP rights. This is clearly the case when it comes to patent litigation surrounding drug approvals.

Patent infringement related to other kinds of sales of pharmaceutical is a little bit more difficult to manage than it is for infringement related to legal sales of pharmaceutical within the United States. For example, generic versions of VIAGRA ordered online that are shipped to the consumer located in the United States from overseas are illegal. In this case, the generic VIAGRA is illegal because it is sold in the United States without FDA approval. It is also illegal because it violates the IP rights of Pfizer, the brand owner. These are related, but fundamentally different reasons they are illegal, and each violation has different implications. With regard to lack of FDA approval, the primary implication of this problem is that the safety and efficacy of the drug is truly unknown. With regard to the IP-rights violations of Pfizer, this is a problem that is monetary and social. However, it is difficult to prosecute against the infringer primarily due to jurisdictional issues.

As an example, sample SING1 analysed as part of this research was purportedly (by package labelling) manufactured in India, shipped from Singapore (by postmarking), and received in the United States. What is the appropriate jurisdiction within which to file action?

Jurisdiction issues challenges not only IP rights in the pharmaceutical industry, but also other industries as well. (Dean, 2013)

It seems one of the best ways, at least in theory, to enforce IP rights protection for violations against United States patents is by way of trade agreements. In the 1980's the United States was undergoing a transformation from an industrial to an information economy. Waning industrial competitiveness hurt United States companies and international trade. The United States began searching for new areas of commerce which would help it maintain competitiveness. IP emerged as "a new basis of comparative advantage." (Subramanian, 1991) There were several IP-related industries, namely the entertainment industry (records and movies), pharmaceutical industry, and the computer industry who were becoming extremely important contributors to the United States economy. Computer technology, for example, was a huge growth industry during the mid-1980s. During this time, personal computers hit the market, computer programs became hot items, and computer software emerged as a commercial product with a high level of economic return. (Halbert, 1997) The United States worked to protect its IP interests and as a result has become the international advocate for strong IP-rights protection. This advocacy has been the motivating force behind the inclusion of IP rights in the general agreement on tariffs and trade (GATT), the United States-Canada free-trade agreement, and the North American free-trade agreement. (Halbert, 1997)

In 2009, the Commissioner of the USPTO stated that his office works closely with the Office of the United States Trade Representative (USTR) and other agencies to establish, on a bilateral and multilateral basis, workable treaty commitments and trade agreements. For example, Commerce worked with the USTR on matters concerning the IP chapter for several free trade agreements (FTAs) during FY 2008, most notably negotiation of the IP chapter of the

United States-Malaysia FTA, Costa Rica's implementation of the Dominican Republic-Central America-United States FTA, Peru's implementation of the United States-Peru Trade Promotion Agreement, as well as implementation of the United States-Chile FTA. Commerce also contributed to the development of the United States' World Trade Organization (WTO) dispute settlement case against China relating to deficiencies in its IP rights enforcement regime. In addition, the USPTO co-chair's the IP Rights Working Group in the United States-China Joint Commission on Commerce and Trade (JCCT), the United States' ongoing trade dialogue with China. (Stoll, 2009)

It can be argued that unless trade agreements mandate the consideration of IP rights by foreign countries, there is virtually no recognition of such rights. (Bird, 2006) For instance, in China and India, coercion attempts by the United States centered on trade agreements were used to get these countries to recognize IP rights. While there is genuine concern about whether or not coercion attempts garner real benefit in the long term, infringement of IP rights in these countries is a significant problem for brand owners. (Bird, 2006) Brazil faced overwhelming pharmaceutical industry pressure and governmental threats of sanctions from the United States to improve its patent protection for drug products and processes. Brazil finally gave up its resistance by discussing IP rights at the GATT, joined the trade-related aspects of IP rights (TRIPS) agreement, and now possesses a functioning patent approval system that is fairly consistent with the minimum standards of protection required by TRIPS. (Schulz & Wu, 2004)

The TRIPS agreement is quite comprehensive in its understanding of the complexity of the IP-protection problem, especially within the pharmaceutical industry. The agreement requires all WTO Member States to grant patents for pharmaceutical products or process inventions for a minimum of 20 years. (Velásquez & Boulet, 1999) Prior to the agreement,

many Member States granted no rights at all, or had terms as short as five years. It also provides time for developing countries to modify and enact laws that made them compliant with the agreement. The agreement also allows the use of compulsory licenses, a provision that demonstrates an understanding of the need for some consideration of public-health crises (even if at the expense of an individual's right to own property). Compulsory licensing enables a competent government authority to license the use of a patented invention to a third party or government agency without the consent of the patent holder. Article 31 of the Agreement sets forth a number of conditions for the granting of compulsory licenses. These include a case-by-case determination of compulsory-license applications, the need to demonstrate prior (unsuccessful) negotiations with the patent owner for a voluntary license, and the payment of adequate remuneration to the patent holder. Where compulsory licenses are granted to address a national emergency or other circumstances of extreme urgency, certain requirements are waived in order to hasten the process, such as that for the need to have had prior negotiations to obtain a voluntary license from the patent holder. (World Health Organization, 2014)

Enforcement of Intellectual Property Rights in Underdeveloped Societies

Even in the best of cases where IP-rights protections are in place like for Member States of the TRIPS agreement, enforcement of these rights is not common. (Bird, 2006) Interestingly, it has been proposed that although social benefits may arise from patent protection through the discovery of new drugs, the TRIPS agreement standards derive from those of industrialized countries and are not necessarily appropriate for the development level of all countries. (Velásquez & Boulet, 1999) As previously mentioned, IP rights are fundamental in a developed society like the United States, but their value is not always appreciated.

It is likely the best chance for success of IP-rights enforcement on a global scale is by way of trade agreements. However, there are other efforts taking place that may lead to the improvement of IP-rights enforcement. The USPTOs Attaché Program was formally instituted in 2006 for the benefit of United States economic and political interests abroad to promote the value and importance of strong IP protection and enforcement in selected, high-profile countries where United States IP challenges are greatest. In partnership with Commerce's more broadly scoped Foreign Commercial Service and the Department of State, the IP Attachés are sent out to strengthen global IP protection and enforcement overseas. The IP-rights experts support United States embassies and consulates on IP-rights issues, including devising strategies to stop counterfeiting and piracy, and supporting United States government efforts to improve the protection and enforcement of IP rights. The Attachés also advocate United States IP policies, coordinate training on IP rights matters, and assist United States businesses that rely on IP-rights protection abroad. These Attachés serve at posts in Brazil, Russia, India, China, Thailand, and the United States Missions in Geneva. (Stoll, 2009)

Although hopeful, it seems lofty to expect that IP-rights enforcement related to pharmaceuticals in countries of extreme poverty will improve in the short term. The unfortunate aspect of this realization is that these environments are the ones where counterfeit drugs pose the greatest short- and long-term threat to public health. (USP Council of the Convention Section on Global Public Health, USP Council of Experts International Health Expert Committee, USP Regionalization Team, Heyman, & Williams, 2011) The administration of counterfeit or substandard drugs is the norm in these regions of the world. In fact, without the availability of counterfeit or substandard drugs, no drugs at all would be available for these citizens, which can be considered a problem if government has a moral responsibility to guarantee its citizens a right

to a healthy life. (Gewertz & Amado, 2004) Some researchers have proposed charging counterfeiters with manslaughter when a patient's death can be directly linked to performance of a counterfeit medication. (Newton, et al., 2006) This approach may help curb the influx of counterfeit goods because it would increase the risk counterfeiters take when supplying these harmful drugs. Currently, the risk/reward ratio for counterfeiters in these regions of the world is so low that there is no incentive to deter these criminals from engaging in these activities. (Thomas, 2011) There have been instances where safe medications have been delivered to these regions of the world, but abuses in these situations are also a big problem that frequently lead to the diversion of these goods from their intended recipients. (Médecins Sans Frontières Australia, 2014)

It seems fair to say that public health is the most significant factor when considering the counterfeit-drug problem, but coupled with this public-health aspect is the need for developed societies to support innovation by enforcing IP rights. Extending this to underdeveloped and extremely poor countries is important. Enforcement is challenging, and in many regions of the world mechanisms are in place to support this enforcement.

CHAPTER 16. FUNDING OF PHARMACEUTICAL RESEARCH

Funding of pharmaceutical research comes from a variety of different sources including private industry, government, not-for-profit organizations, and individual donors. The cost of research and development, by all accounts, is high. In 2003, DiMasi and colleagues reported in the *Journal of Health Economics* that the pre-approval cost estimate for development of a drug in the United States is \$802 million (year 2000 United States dollars). (DiMasi, Hansen, & Grabowski, 2003) Since this time, this number has been cited frequently.

In addition to the cost estimate, these authors determined that the average successfully developed new molecular entity (NME) in the study's sampled required 4.3 years for discovery and preclinical development, and another 7.5 years for clinical trials and FDA approval. Approval itself took an average of 1.5 years. Thus, developing an NME and bringing it to market required 11.8 years, on average. (DiMasi, Hansen, & Grabowski, 2003) Table 11 summarizes estimated costs calculated in the study, as well as average research length for both preclinical and clinical phases of development. The study surveyed drugs from a representative set of therapeutic classes, but it excluded some types of new drugs that have lower average research and development costs. In addition, the estimate may not be representative of research and development costs for smaller pharmaceutical firms which did not participate in the survey on which the study was based. However, by focusing on NME's, the study did base its cost estimate on the types of drugs that have been the source of most pharmaceutical breakthroughs. (Congressional Budget Office, 2006)

DiMasi and Others' Estimate of Average Research Costs and Times for Successfully Developed New Molecular Entities

	Average Length of Research Phase		
	Preclinical Phase (4.3 years) ^a	Clinical Trials and FDA Approval (7.5 years)	Total (11.8 years)
Research and Development Costs (Millions of 2000 dollars)			
Direct costs	121	282	403
Opportunity costs ^b	214	185	399
Total Costs	335	467	802

Source: Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics*, vol. 22, no. 2 (March 2003), pp. 151-185.

Note: FDA = Food and Drug Administration.

- The estimate for the duration of the preclinical phase is based on the comprehensive drug database maintained by the Tufts University Center for the Study of Drug Development.
- Opportunity costs are the costs associated with keeping capital tied up in a specific drug-development project for a given period (that is, the forgone interest or earnings that a company might have gained from investing its capital in other ways). DiMasi and others assumed the forgone rate of return to be 11 percent per year.

Table 11. Estimated costs calculated by DiMasi et al. Reprinted from Congressional Budget Office Report, *Research and Development in the Pharmaceutical Industry*, 2006.

Although this study is widely cited, it is not without its critics. Light and Warburton discuss various reasons for the problems with the calculation of this \$802-million value. They state, among other things, that this cost figure, like the ones that preceded it, is based on confidential, unsystematic data, and has dubious scientific validity. (Light & Warburton, 2005) They state that given the many independent sources of variability, any point estimate is misleading. Reporting that research and development costs of major new drugs range from \$300 million to \$1.3 billion rather than a single average point estimate, therefore, is more informative. (Light & Warburton, Setting the record straight in the reply by DiMasi, Hansen and Grabowski, 2005)

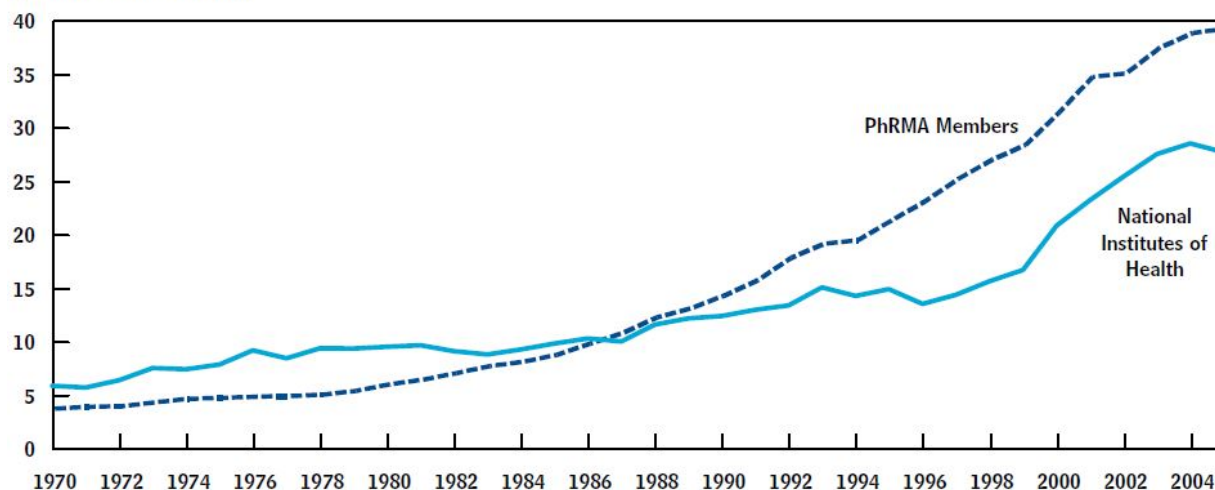
While the exact cost of pharmaceutical research and development is an elusive number to determine, it is clear that regardless of how costs are calculated, the numbers are high and

usually in the hundreds of millions of dollars. (Adams & Brantner, 2006; Light & Warburton, 2011) For every successful new drug, a firm will have had many failed drug projects that did not survive clinical trials or that never won approval from the FDA. Estimates of average research and development costs per drug include the costs of those failures. (Congressional Budget Office, 2006)

These high costs have been used by the pharmaceutical industry for decades to justify high sale prices. (Melethil, 2005) When you follow the money, it seems that the largest percentage of research and development costs is, indeed, paid by industry. Government makes a significant contribution, though. Health-related research receives the second largest amount of federal support for research and development (behind only defense-related research). That support has been steadily growing for several decades. Spending on research by the National Institutes of Health (NIH)—by far the primary recipient of government funding for health-related basic research—was \$5.8 billion (in 2005 dollars) in 1970. This figure more than doubled to \$12.3 billion by 1990. By 2004, it reached \$28.5 billion. In comparison, spending reported on research and development by the members of the Pharmaceutical Research and Manufacturers of America (PhRMA) was just two-thirds the size of NIH's spending in 1980. PhRMA's research and development spending surpassed NIH's in 1987 and has remained higher since then, although both grew at similar rates in the late 1990s and early 2000s. Figure 69 shows the spending data from 1970 to 2004. (Congressional Budget Office, 2006)

Annual Spending on Research and Development by Drug Companies and the National Institutes of Health

(Billions of 2005 dollars)



Source: Congressional Budget Office based on Pharmaceutical Research and Manufacturers of America, *Pharmaceutical Industry Profile 2006* (Washington, D.C.: PhRMA, March 2006); and National Science Foundation, *Federal Funds for Research and Development* (various years), available at www.nsf.gov/statistics/fedfunds/.

Note: Spending was adjusted for inflation using the biomedical research and development price index from the Bureau of Economic Analysis.

Figure 69. Research and development spending between 1970 and 2004 for PhRMA members and NIH.

Government funding has a very strong role in pharmaceutical research and development, but it tends to have a different role than funding from private industry. Much of the government funding is for the basic research on disease mechanisms that underlie the search for new drugs. Although the distinction between basic and applied research and development is not always clear, it is useful to think of basic research as generating information or knowledge that is not readily embodied in physical products. Federally supported basic research in genomics, molecular biology, and other life sciences has greatly expanded the drug industry's technological opportunities, stimulating private investment in pharmaceutical research and development. (Congressional Budget Office, 2006)

The rationale for government funding of basic scientific research is simple; if such research was left solely to the private sector, too little of it would be done. The benefits to society from doing additional basic research and development (beyond what firms alone would conduct) far outweighs the costs. A company's incentive to invest in research and development is limited to its own expected returns. In the case of basic research and development, those returns can be particularly low compared with the social benefits. It can be difficult for private companies to capture more than a small fraction of the total social value of their basic research. A basic research discovery cannot be patented unless the inventor can credibly describe the discovery's "specific and substantial" utility. (Congressional Budget Office, 2006) It seems the role government funding plays is to create new knowledge and new tools and produce large numbers of highly trained researchers, all of which are a direct and important input to private-sector research. (Cockburn & Henderson, 2001)

Some argue that since government funding can be linked to drug products that provide profit to private industry, government should share in the profits. This approach has historically not been met with success. Prior to 1980, invention rights supported by government agencies belonged strictly to the federal government. Nobody could exploit such research without tedious negotiations with the federal agency concerned. Worse, companies found it near impossible to acquire exclusive rights to a government-owned patent. Without these rights, few firms were willing to invest millions more of their own money to turn a raw research idea into a marketable product. The result was that inventions and discoveries made in American universities, teaching hospitals, national laboratories, and non-profit institutions sat in warehouses gathering dust. Of the 28,000 patents that the American government owned in 1980, fewer than 5% had been

licensed to industry. Although taxpayers were footing the bill for 60% of all academic research, they were getting hardly anything in return. (Innovation's golden goose, 2002)

The transfer of rights from the government to the inventor and university came about in 1980 with the Bayh-Dole Act. The philosophy behind the Act was the belief that the solution lay with the individual and that the best thing government could do to provide incentives for success was get out of the way of these individuals. (Stevens, 2004) Government would then benefit in two ways. First, the therapeutic value of new medications would be considered a primary benefit to government. (Congressional Budget Office, 2006) Second, even though rights were transferred from government to individual researchers and universities, some financial benefits to government were written into the law to help the government get better results from their funding than had historically been the case. Even so, the government has not had much success collecting on these financial incentives primarily due to its own administrative issues. (Gerth & Stolberg, 2000)

The Bayh-Dole Act was designed to push federally financed research from the university laboratory into the marketplace. Scientists who made discoveries using taxpayer money were required to file invention reports with the government. Universities were directed to license patented inventions to companies that would commercialize them. The law was originally passed to aid small businesses, but later it was modified so that even big companies could benefit. If a company did not develop a product quickly enough, the government could revoke the company's license and hand the job over to a competitor. It could also take control of an invention to alleviate "health or safety needs," the law said. (Gerth & Stolberg, 2000)

Once an invention is on the market, the law grants the government the right to buy it without paying customary royalties. At the same time, other laws enable federal agencies to put

taxpayer-financed inventions out to competitive bidding. For example, the government could give other companies (besides the developer) the opportunity to manufacture and sell at a lower price, but only to the government. However, in the first 20 years after the Bayh-Dole bill became law, the government had not taken advantage of these provisions. One reason is because the government already buys drugs cheaply by purchasing them in bulk. More importantly, even if federal officials wanted to use the Bayh-Dole Act to get medicines at still cheaper prices, they could not because they do not keep track of products, including drugs that are invented with taxpayer money. In addition, a preliminary report by the inspector general's office of the Department of Health and Human Services found that as many as 22 percent of discoveries financed by the health institutes were not reported by universities, as is required. More than 2,000 inventions developed with government money were reported to the health institutes in 1999, but agency officials said in interviews that they had no idea which, if any, companies had licensed those inventions, or how they were being used. (Gerth & Stolberg, 2000)

In spite of the government's inability to fully collect financially from the drug products it funds, the Bayh-Dole Act did invigorate industry. Coming out of World War II, the United States was unchallenged in its political and economic leadership of the free world. However, by the end of the 1970s it was clear that United States industry had lost its international competitiveness to Europe and, particularly, to Japan. This process had started with the success of the United States programs to rebuild its Allies and former enemies and was completed by the impact of the oil shocks of the 1960s and 1970s on an economy dependent on cheap domestic energy. Examples of the loss of competitiveness abounded. The United States lost leadership roles in both mature industries, such as automobiles and televisions, and emerging industries, such as memory chips. In addition, Japanese companies dominated in industries based on

American and European innovations, such as video cassette recorders and compact discs. The Bayh-Dole Act was intended to reverse this trend toward non-competitiveness. It is unlikely that anyone in the technology-transfer community would dispute its importance. (Stevens, 2004)

Although initially the concern with this Act was that the government would provide investment and not reap reward, it seems the most important criticism is the impact it has had on academic institutions and their role in society. Many scientists, economists, and lawyers believe the Act distorts the mission of universities, diverting them from the pursuit of basic knowledge, which is freely disseminated, to a focused search for results that have practical and industrial purposes. Whether that is a bad thing is a matter of debate. (Bayhing for blood or Doling out cash? Intellectual property, 2005)

What is not in dispute is that it makes American academic institutions behave more like businesses than neutral arbiters of truth. For example, a study published in 2003 by Jerry and Marie Thursby of Emory University and the Georgia Institute of Technology, respectively, reported that a survey of industry licensing executives shows 27% of their university licenses include clauses that allow deletion of information from papers before submission, and 44% ask for publication delay (3.9 months on average) (Thursby & Thursby, 2003)

Moreover, there is ample evidence that scientific research is being delayed, deterred, or abandoned due to the presence of patents and proprietary technologies. Researchers (and particularly their minders in university patent-licensing offices) are increasingly reluctant to share materials and knowledge with others unless such sharing is accompanied by legal agreements about "reach-through" royalties on potential findings and the right to restrict publication of results. A study released by the American Association for the Advancement of Science noted that 35% of academic biotechnology researchers experience difficulties getting

hold of patented technologies that they need for their work, even though non-commercial research is supposed to be exempt from the normal restrictions of patents. The question is just how "non-commercial" is such research? Lawsuits between universities and researchers over patents and royalties are now common. (Bayhing for blood or Doling out cash? Intellectual property, 2005)

Even industry is starting to complain about a gold-digger mentality among academic administrators. The most notorious example is Columbia University, which tested the boundaries of the law by seeking to re-patent a technique whose patent had already expired. The patent was for a technology called co-transformation that is used to place external DNA into cells, and is important in making certain drugs. Columbia eventually backed down, but only in the face of both public criticism and a series of writs from biotechnology companies. (Bayhing for blood or Doling out cash? Intellectual property, 2005)

Another case ensnared the University of Utah, which licensed its patent on a gene underlying hereditary breast cancer exclusively to one company, Myriad Genetics. That gave Myriad Genetics a monopoly on diagnostic testing for the disease, which was controversial enough. Then the firm started suing universities that were using its technology in follow-up research, bringing the non-commercial research exemption still further into question. (Bayhing for blood or Doling out cash? Intellectual property, 2005)

Funding has changed in recent years. Neither federal nor private support for research and development is likely to return to the trend that produced a tripling in support between 1995 and 2005. As a portion of gross domestic product, research and development expenditures are declining in the United States and Europe, whereas they are increasing at an accelerated rate in China, South Korea, and India. (Moses III & Dorsey, 2012) In 2009, privately funded

biomedical research comprised \$70 billion (65%) of the \$110 billion total. (Dorsey, et al., 2010)

The NIH budget has not kept pace with inflation. The result is justified concern over the support of institutions and researchers who must conduct critical early-stage investigations to validate new approaches to diseases of high prevalence and high morbidity such as common cancers, autism, and dementia, for which the public health burden (and costs) are increasing, and effective prevention or treatment are elusive. (Moses III & Dorsey, 2012)

New drugs have revolutionized the treatment of ulcers, stroke, and various psychiatric conditions. They have dramatically improved the quality of life of asthma sufferers. They have brought the symptoms of AIDS under control for a significant fraction of the infected population. Some cancers are now reliably curable by drug therapy, and new drugs for hypertension and high cholesterol are proving instrumental in the treatment of heart disease, still the largest killer of Americans. Drugs "in the pipeline" promise major advances in the treatment of arthritis, Alzheimer's disease, many kinds of cancers and a variety of other chronic conditions. (Cockburn & Henderson, 2001) These innovations are expensive. Cost required to invent and develop these innovations is a serious consideration.

The cost of innovation is expensive and drug companies argue that without profit incentive, the risks would be too high to invest in development. However, there is concern by some that the amount of profit of some successful pharmaceutical companies is too high making it impossible for some patients to be treated. In 2013, a group of over 100 oncologists discussed the exorbitant cost of innovative cancer medications in a commentary piece in the journal *Blood* of the American Society of Hematology. (Experts in Chronic Myeloid Leukemia, 2013) They propose that these costs are not justified and may even be immoral. The authors report that the annual sale of imatinib, a blockbuster drug used to treat chronic myelogenous leukemia, was

approximately \$4.7 billion dollars in 2012. They propose this targeted cancer therapy may have set the pace for the rising costs of cancer drugs. Initially priced at \$30,000 per year when it was released in 2001, the annual cost in 2012 at \$92,000, in spite of the fact that all research costs were accounted for in the original proposed price and recovered within the first two years the drug was on the market. (Experts in Chronic Myeloid Leukemia, 2013)

The doctors who signed on to the commentary are not alone in their criticism of pricing by pharmaceutical companies. Some of these doctors said they were inspired by physicians at the Memorial Sloan-Kettering Cancer Center in New York, who refused in 2012 to use a new colon cancer drug, Zaltrap®, because it was twice as expensive as another drug without being better. After those doctors publicized their objections in an Op-Ed article in The New York Times (Bach, Saltz, & Wittes, 2012), Sanofi, which markets Zaltrap, effectively cut the price in half. (Pollack, 2013)

Development for cancer therapy's tend to be higher than for other types of innovative drugs, but It is important that the pricing of these goods by pharmaceutical manufacturers be considered when evaluating cost. A determination of what is unreasonable profit should be considered when the consequence of high prices is that access to life-saving medication is denied. In the case of the drug imatinub, it is clear that profits are high.

Pfizer, the manufacturer of VIAGRA, has also been experiencing increase in profits in recent years. Table 12 shows Pfizer's profit in the form of net income attributable to Pfizer Inc. (% of revenues) for the years 2011 through 2013. This value increased from 16.4% to 26.7% from 2011 to 2012, up to 42.7% for the year 2013. (Pfizer Inc. and Subsidiary Companies, 2013)

ANALYSIS OF THE CONSOLIDATED STATEMENTS OF INCOME

(MILLIONS OF DOLLARS)	Year Ended December 31,			% Change	
	2013	2012	2011	13/12	12/11
Revenues	\$ 51,584	\$ 54,657	\$ 61,035	(6)	(10)
Cost of sales	9,586	9,821	12,500	(2)	(21)
% of revenues	18.6%	18.0%	20.5%		
Selling, informational and administrative expenses	14,355	15,171	17,581	(5)	(14)
% of revenues	27.8%	27.8%	28.8%		
Research and development expenses	6,678	7,482	8,681	(11)	(14)
% of revenues	12.9%	13.7%	14.2%		
Amortization of intangible assets	4,599	5,109	5,465	(10)	(7)
% of revenues	8.9%	9.3%	9.0%		
Restructuring charges and certain acquisition-related costs	1,182	1,810	2,841	(35)	(36)
% of revenues	2.3%	3.3%	4.7%		
Other (income)/deductions—net	(532)	4,022	2,486	*	62
Income from continuing operations before provision for taxes on income	15,716	11,242	11,481	40	(2)
% of revenues	30.5%	20.6%	18.8%		
Provision for taxes on income	4,306	2,221	3,621	94	(39)
Effective tax rate	27.4%	19.8%	31.5%		
Income from continuing operations	11,410	9,021	7,860	26	15
% of revenues	22.1%	16.5%	12.9%		
Discontinued operations—net of tax	10,662	5,577	2,189	91	*
Net income before allocation to noncontrolling interests	22,072	14,598	10,049	51	45
% of revenues	42.8%	26.7%	16.5%		
Less: Net income attributable to noncontrolling interests	69	28	40	146	(30)
Net income attributable to Pfizer Inc.	\$ 22,003	\$ 14,570	\$ 10,009	51	46
% of revenues	42.7%	26.7%	16.4%		

Certain amounts and percentages may reflect rounding adjustments.

* Calculation not meaningful.

Table 12. Analysis of the consolidated statements of income of Pfizer for the years 2011 through 2013.

Pfizer stock prices have also increased steadily over the past five years. Over the past ten years, these stock prices were at their lowest in the year 2009 (approximately \$12.5 per share) and at their highest in the year 2004 (approximately \$35 per share). Current stock prices are approximately \$30 per share. (Pfizer, 2014) Pfizer stock prices for the past 10 years are shown in figure 70.

Historical Stock Chart



Figure 70. Historical stock chart of Pfizer stock.

Pricing and evaluation of profit is an important consideration. Incentive to invest in pharmaceutical innovation is critical and impacted by counterfeit drugs. However, review of the profit margins need to be considered. Pharmaceutical companies have been criticized for their practices used to set sale prices by educated health-care professionals with regard to certain types of innovative drugs. (Bach, Saltz, & Wittes, 2012; Experts in Chronic Myeloid Leukemia, 2013) This is an important consideration that needs to be addressed for appropriate solutions to be proposed.

CHAPTER 17. LONG-TERM THREAT OF COUNTERFEIT DRUGS TO PUBLIC HEALTH

Counterfeit drugs pose a serious long-term threat to public health. The theft of this pharmaceutical IP is reducing the financial incentive to drug companies to invest in innovative research. If investors in these private firms can't rely upon the legal and justice systems to enforce their IP rights, it is likely they will no longer invest in this expensive and risky business. The United States government has historically shown that it does not have the capability to bring a new and innovative pharmaceutical product to the market without support from private industry. In addition, government funding of research in the basic sciences will likely not be as strong as it has been in the past. This will require additional funding from private investments in an environment that is much less likely to rally investors.

There is no question that pharmaceutical innovation is a valued and necessary component of developed society. Patenting and protection of patent rights has provided incentive to investors. Patenting is an integral part of the drug-development process in the United States. The patent system is fully integrated with federal regulations throughout the process, and laws are in place that balance the patent owner's rights with the value of their innovations to society. Further, government funding supports basic research and transfers to patent inventors the rights of the work product of these funds.

Laws are also in place to allow for enforcement of IP rights in the United States. These laws, coupled with extensive FDA regulation designed to provide a safe and effective drug supply chain, have made the short-term issues of counterfeit drugs in the United States less problematic than in other regions of the world. In these other regions, trade agreements or other methods to establish patent protection must be enforced so that the financial incentive to private investors is maintained.

The United States has taken a leadership role in the development of pharmaceutical innovations that have benefitted the rest of the world. While it has had success in the United States with protection of these rights, infringement throughout much of the world is rampant. This infringement cuts into profits of pharmaceutical innovators, and minimized the rewards to investors. Without private investment, the United States will likely move away from the leadership role it has taken. This will seriously threaten the future of pharmaceutical innovation. There is currently no reasonable replacement to serve in the role the United States takes as pharmaceutical innovators. In an environment where infringement of IP rights related to these innovations throughout the world is accepted, the system upon which pharmaceutical innovation is built will not sustain itself. The burden of payment for pharmaceutical innovation will need to be shared more evenly with societies in other regions of the world.

CHAPTER 18. THE VALUE AND CONTRIBUTION OF THIS RESEARCH TO FORENSIC SCIENCE AND CRIMINAL JUSTICE

Counterfeit drugs are a problem for criminal justice. Theft of intellectual property in the pharmaceutical industry has caused sickness and death (Newton, et al., 2006; World Health Organization, 2008; Wondemagegnehu, 1999). It is necessary that the perpetrators of these crimes are brought to justice. In some cases, threats to health and safety are short term; in others they are long term. This research describes these threats in detail.

The problem is complex, and there are many important factors that need to be considered to successfully address the problem. Public-health challenges, drug-development challenges, legal challenges, and financial considerations are all important aspects of the problem that need to be understood. The counterfeit-drug problem integrates forensic science, patent law, enforcement of patent rights, pharmaceutical innovation, and public-health issues. This research is valuable to criminal justice because it details these aspects so that appropriate solutions to the problem can be proposed.

This research defines the problem counterfeit drugs present and why they are a problem for the criminal justice system. It also describes the complexity the problem. The critical aspects of each of these topics related to the counterfeit-drug problem are presented. Understanding these topics is needed by the criminal justice system to understand the complicated nature of the counterfeiting problem, and why IP rights in the pharmaceutical industry are so vitally important and need to be enforced. This research summarizes in a systematic way, all of these integral aspects of the counterfeit-drug trade providing the background necessary to understand and address this problem.

This project is also important to forensic science. Forensic science is the application of the natural sciences to matters of the law. The laws in effect at any given time are usually

influenced by or derived from those of previous periods. (De Forest, Gaensslen, & Lee, 1983)

Laws in the United States related to drug development and pharmaceutical innovation have changed dramatically since 1980. These changes, coupled with the advent of the internet and other globalization that has taken place over this same time period, have forged a new discipline within the field of forensic science. Societal and public-health needs require that forensic scientists and other practitioners of justice provide the tools to successfully investigate, identify, and adjudicate criminal violators of IP rights, especially with regard to pharmaceuticals. It defines the challenges faced by the field of forensic science and proposes methods that may be used to address these challenges. This will enable forensic scientists to provide support to law enforcement and other members of the legal system to successfully investigate and adjudicate these crimes.

Forensic scientists are tasked with providing investigative leads to identify counterfeiters, as well as with providing scientific assessments of evidence that can be used during adjudication of these crimes. This research explored the use of field-portable instruments based upon technologies with high discrimination potentials to help forensic scientists meet these goals. Detection in the field is an important capability because when decisions about a product's authenticity can be quickly made at a port of entry, that article can be confiscated before it enters the legitimate supply chain. The ability to stop the entry minimizes risk to the consumer.

This research also proposed a method to help scientists share data collected in the field, helping to define the role forensic scientists play in the solution to this problem. One of the major challenges to forensic scientists when establishing provenance of counterfeit drugs is the limited sample set available for analysis. The method proposed as a result of this research would allow users across the globe to share useful scientific data from samples tested. Forensic

scientists would then have access to large numbers of samples from distant regions of the world. These shared data could be used for comparisons, to evaluate trends, and perform other types of data review useful in establishing provenance.

CHAPTER 19. REFERENCES

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