

ABSTRACT

Title of Document: AN ANALYSIS OF PHARMACEUTICAL
COUNTERFEITING: ASSESSING
SCREENING FACTORS AND THEIR
INFLUENCE ON COUNTERFEITING

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The United States pharmaceutical supply chain is one of the safest and most secure systems in the world. However, in recent years, an increasing number of drug counterfeit products were detected in it. This increase in documented incidents greatly concerns the pharmaceutical industry, and state and federal regulatory bodies. The repercussions of a tainted drug supply chain are potentially economically devastating and detrimental to the health and well-being of the public. Decision makers face a challenge keeping the drug supply chain safe from these influences, specifically assessing the risk of drug counterfeiting. With the problems posed by counterfeit, the identification of the right counterfeit attributes and the development of models to help supply chain managers determine the probability of counterfeit drugs are vital. Known drug counterfeiting research and studies are limited in scope; and despite increasing trends in counterfeiting, empirical research in this area is scarce. This research undertakes an in-depth

examination of literature to identify counterfeit attributes and factors as well as to develop a drug counterfeit model to assess the probability of the drug counterfeiting. The identification of drug counterfeiting attributes resulted from a comprehensive review of the literature and a survey of experts. Data were subsequently collected on the attributes identified through literature, case studies, and experts.

The findings of this research led to these substantive outcomes:

- The identification of 10 key counterfeit attributes: Average Price, Drug Class, Medication Class, Product Type, Volume, Product Complexity, Product Location, Region, Previous Product Counterfeiting, and Product Shortage.
- Using exploratory factor analysis, a model emerged with three distinct factors: Market, Product History, and Supply Chain Characteristics.
- A process and a model are developed to assess the probability of drug counterfeiting. This is the first known model developed to assess the probability of drug counterfeiting.

Decision makers can assess products in an objective and robust way to determine which products are of greater risk of counterfeiting, and to develop policies and strategies to mitigate or minimize counterfeit drugs in the legitimate supply chain.

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AN ANALYSIS OF PHARMACEUTICAL COUNTERFEITING: ASSESSING
SCREENING FACTORS AND THEIR INFLUENCE ON COUNTERFEITING

By

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Dedication

I dedicate this dissertation to my loving wife, Nichole and my parents, Abdool and Nazaneen.

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To Dr. Baecher, I express my sincere appreciation and gratitude for his immense guidance and support while undertaking and writing this dissertation. You are an extraordinary mentor and professor.

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I thank GOD for giving me the energy and inspiration.

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Chapter 1: Introduction

1.1 Background and Motivation

The United States pharmaceutical supply chain is one of the safest and most secured systems in the world (Lutter, 2006). However, in recent years, an increasing number of drug counterfeit products were detected in the supply chain. This increase in documented incidents is of great concern to the pharmaceutical industry, and state and federal regulatory bodies. The repercussions of a tainted drug supply chain are potentially devastating not just economically but also to the health and well-being of the public. The need exists for proactive methods to help supply chain managers or regulatory risk managers assess the probability of counterfeit drug products in the legitimate pharmaceutical supply chain (PSC).

The counterfeiting of pharmaceuticals extends beyond borders and is a global problem. Globalization and pharmaceutical manufacturing outsourcing significantly contributed to the increased volume of imported drugs into the United States and the global surge in counterfeiting (see Figure 1), especially in countries that are more involved in pharmaceutical manufacturing (Liu, 2012).

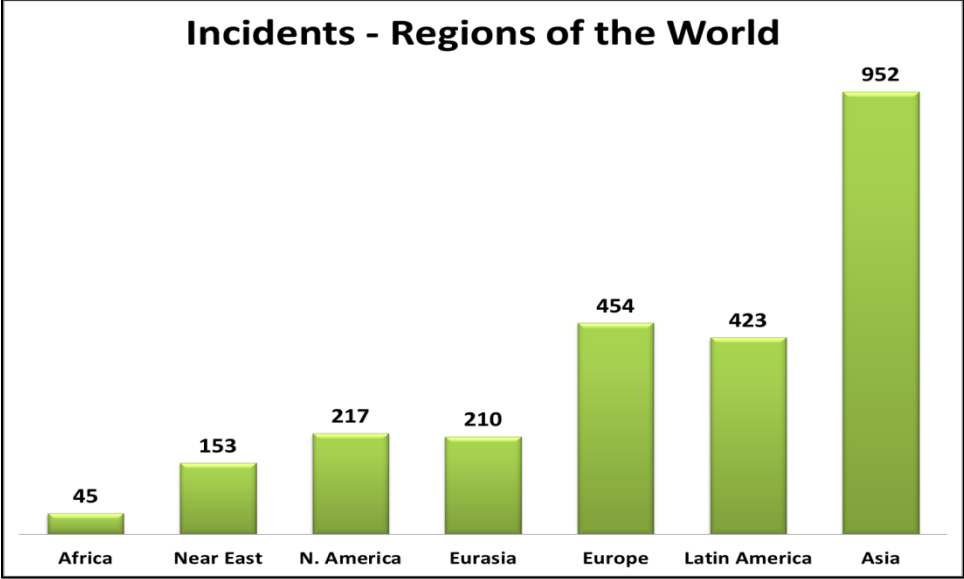


Figure 1: Global Counterfeits Incidents (PSI, 2014)

According to the Pharmaceutical Security Institute (PSI, 2014), counterfeiting of pharmaceuticals has steadily increased since 2002. In 2012, 2018 counterfeiting incidents were recorded by PSI (see Figure 1). Of these, 41 % (841) were discovered by Customs through seizures or police/health raids (see Figure 2).

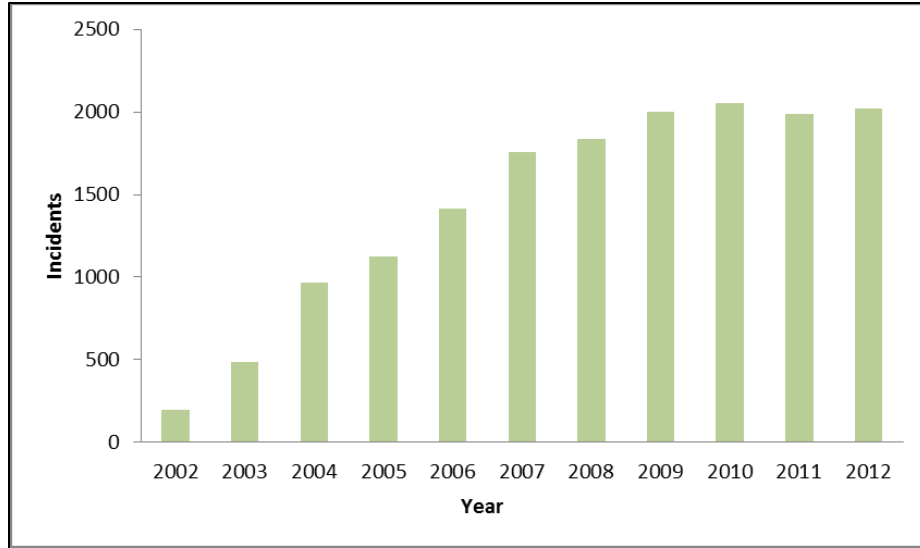


Figure 2: Number of Counterfeiting, Illegal Diversion and Theft Events from CY2002 to CY 2012 (PSI, 2014)

Also, of the counterfeit seizures taken by Customs or as a result of police/health inspector raids in CY 2012, 52% were commercial and 40% were non-commercial (see Figure 3).

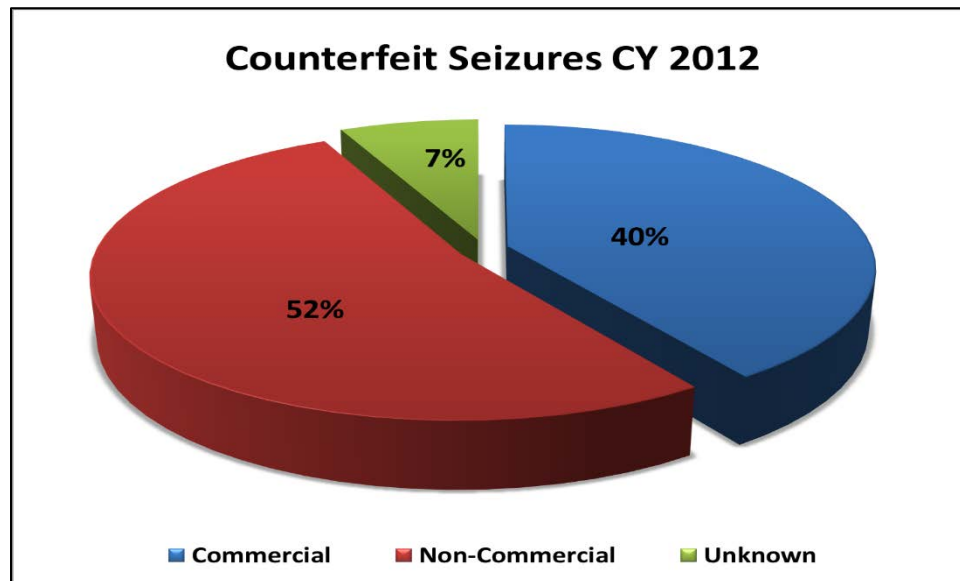


Figure 3: Percentage of Counterfeit Seizures in CY 2012 taken by customs or police/health inspectors (taken from PSI)

Keeping the nation's drug supply safe and effective includes keeping a vigilant eye on all stages of the pharmaceutical process, from acquiring the active pharmaceutical ingredients (APIs) to importation and distribution of the finished dosage form (FDF) drug products into the country. The Food and Drug Administration (FDA) is one agency responsible for keeping the nation's drug supply safe and effective. In doing so, the FDA will need advanced analytical methods and processes to detect and deter counterfeit drugs entering the legitimated supply chain.

The complexity of the global supply chain inherently introduces risks (counterfeiting, theft, nature-disasters, technological accidents, malicious events, etc.) that impact the quality of the drug supplies in the United States. Decision makers face a challenge keeping the drug supply chain safe from these influences, specifically assessing the risk of drug counterfeiting.

Counterfeit drugs are a global pandemic. In 2009, FDA estimated that in parts of Asia, counterfeit drugs accounted for more than 50 percent of medicinal sales, and resulted in the deaths of several thousand people every year (Paul, 2009). Several counterfeit cases originating from Asia, resulted in mortalities from poisonous pharmaceutical ingredients flowing into the global market through traders and intermediaries, who form a supply chain that stretched from small factories in rural China to consumers around the world.

A report published by General Accountability Office (GAO) in 2005 on prescription drugs indicated that, "*FDA officials have stated that they cannot provide assurance to the*

public regarding the safety and quality of drugs purchased from foreign sources, which are largely outside their regulatory system....” (GAO, 2011).

1.2 Significance of the Problem

It is imperative that the United States pharmaceutical supply chain provides safe and effective drugs to consumers. Since 2000, an increasing number of Americans have received counterfeit medicines from legitimate pharmacies (Eban, 2005). These counterfeit medicines look similar to the legitimate product. They are delivered in packaging that are identical to the authentic product, all of this unbeknownst to pharmacists and medical professionals. The gray markets through which these medicines travel easily, obscure their origin. Cherici et al (2011) describes the gray market as a supply channel for unofficial, unauthorized or unintended manufacturer. For example, products that are scarce or short in supply, gray markets may enter or evolve to sell the item at any price the market will bear. In addition, gray markets also compete with innovator’s product by selling products at a lower cost.

Without readily available methods or ability to ensure purity and legitimacy, counterfeit drugs pose a serious risk. These drugs, traveling the gray markets, can be less effective than legitimate drugs and can lead to sinister outcomes such as serious health impact or death. With the problems posed by counterfeit drugs it is vital that the right counterfeit attributes are identified and that models are developed to help supply chain managers determine the likelihood of counterfeit drugs.

1.3 Research Objective and Methodology

The objective of this dissertation is to (1) identify and analyze the factors that can be utilized to assess the probability of drug counterfeiting in the pharmaceutical supply chain (PSC), and (2) develop a counterfeit drug model to help supply chain risk managers (SCRMs) rank drug products by their likelihood of being counterfeit.

Research in drug counterfeiting is limited in scope and provides high-level overview of drug counterfeiting. Despite increasing trends in counterfeiting, empirical research in this area is scarce. Sodipo's (1997) research related to Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) provides a list of attributes influencing counterfeiting. Spink's (2009) research on anti-counterfeiting strategies and a product risk model used Sodipo's risk factors, however, in both research, factors significance as they related to drug counterfeiting was not explored.

To date, current methods fail to adequately identify critical factors and to develop a model to evaluate the likelihood of product counterfeiting within the PSC. Most methods focus on disruptions and optimization in the supply chain, with limited focus on drug counterfeiting. This research undertakes an in-depth examination of literature to identify counterfeit factors as well as to develop a drug counterfeit model to assess the likelihood of the drug counterfeiting.

Figure 4 shows the framework utilized in this research. This includes a comprehensive review of the literature and expert survey, which was conducted to identify attributes

pertaining to drug counterfeiting. Data were subsequently collected on the attributes that were identified through literature, case studies, and experts. An explanatory factor analysis method was used to analyze the counterfeit attributes. A drug counterfeit model is developed and validated with limited available data to determine the probability of drug counterfeiting.

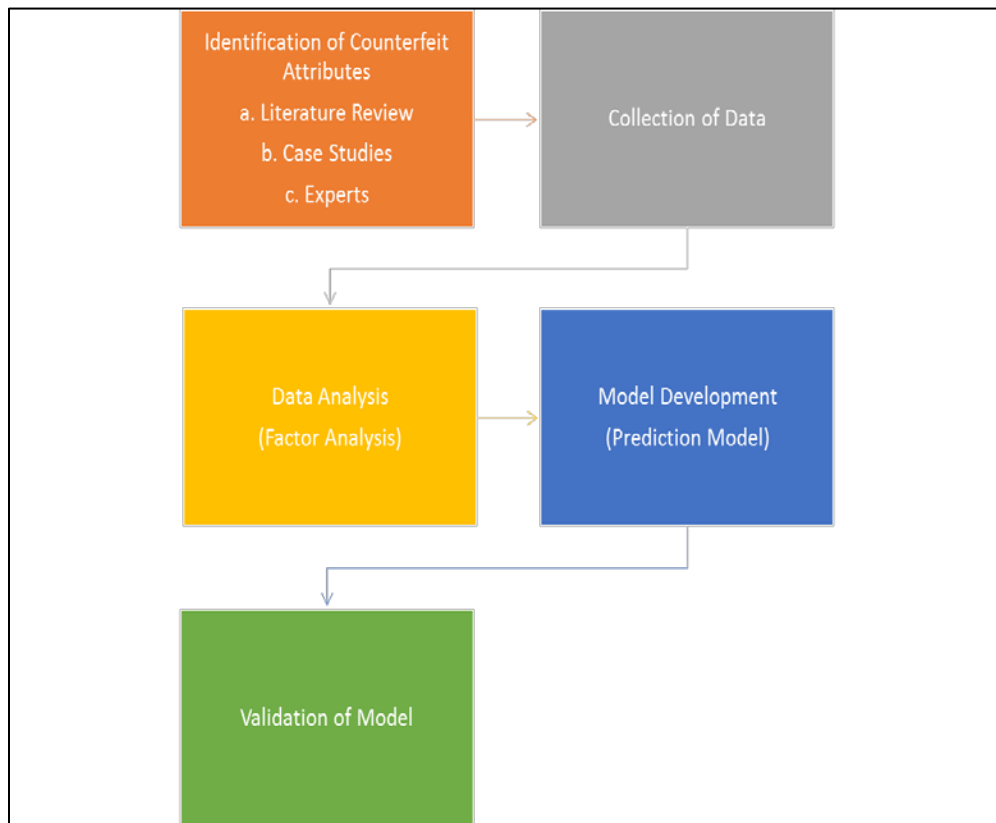


Figure 4: Research Process

1.4 Research Contribution

This research adds to the body of knowledge in a number of ways. First, it identifies, and provides an analysis of the attributes that affect drug counterfeiting. Second, this research develops a counterfeit drug model for ranking drug products at greatest risk of counterfeiting. Prior to this research, there were no known studies to the author knowledge, that adequately identified and analyzed counterfeit attributes and effectively described their effects on the probability of drug counterfeiting. Additionally, the drug counterfeit model developed in this dissertation can be used by supply chain, project, and regulatory risk managers to help allocate resources for drug product testing based on the probability of drug counterfeiting.

1.5 Dissertation Outline

The remaining chapters of this dissertation are organized as follows:

- Chapter 2 provides a review of the literature produced by previous research related to counterfeit attributes for drugs as well as other products. New and emerging trends in drug counterfeiting from a pharmaceutical supply chain are discussed.
- Chapter 3 provides a discussion of the research methodology used for the collection and analysis of counterfeit attributes. This chapter highlights the importance of each counterfeit attribute.
- Chapter 4 describes the data collection methodology and provides a descriptive summary of the data.

- Chapter 5 explains the explanatory factor analysis approach and uses this approach to analyze counterfeit attributes interrelationships. Regression analysis is applied to determine the significance of each factor.
- Chapter 6 explains and develops a drug counterfeit model for determining the probability of counterfeiting.
- Chapter 7 explains a Bayesian Uncertainty analysis framework and applies the framework to improve model prediction. Model validation is presented with known drug counterfeit cases and cases that were not counterfeits.
- Chapter 8 discusses research implications for the drug industry (public and private entities) and discusses limitations of the research and recommendations for future work.

Chapter 2: Literature Review

2.1 Introduction

This chapter provides a literature review on pharmaceutical product counterfeiting and describes the trends, definitions of counterfeiting, and provides a summary of counterfeit attributes.

2.2 Drug Counterfeit Definition

According to the Food and Drug Administration (FDA),

“U.S. law defines counterfeit drugs as those sold under a product name without proper authorization. Counterfeiting can apply to both brand name and generic products, where the identity of the source is mislabeled in a way that suggests that it is the authentic approved product. Counterfeit products may include products without the active ingredient, with an insufficient or excessive quantity of the active ingredient, with the wrong active ingredient, or with fake packaging”, (FDA, 2013).

The World Health Organization (WHO) defines counterfeit medicine or drugs as “...one which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeits products may include products with the correct ingredients or with the wrong ingredients, without

active ingredients, with insufficient active ingredients or with fake packaging (WHO, 2012).”

2.3 Drug Counterfeiting: Global Problem

Counterfeit drugs, both prescription and over-the-counter are a worldwide epidemic and a threat to public health (Martino et. al 2010) (Figure 5.0). According to Martino, “counterfeiting also constitutes an economic problem for legitimate drug manufacturers, undermining their revenues and reputation....The global trade in counterfeit medicines is vast and growing as it is as hugely lucrative business owing to the continued high demand for cheap medicines and low production costs.”

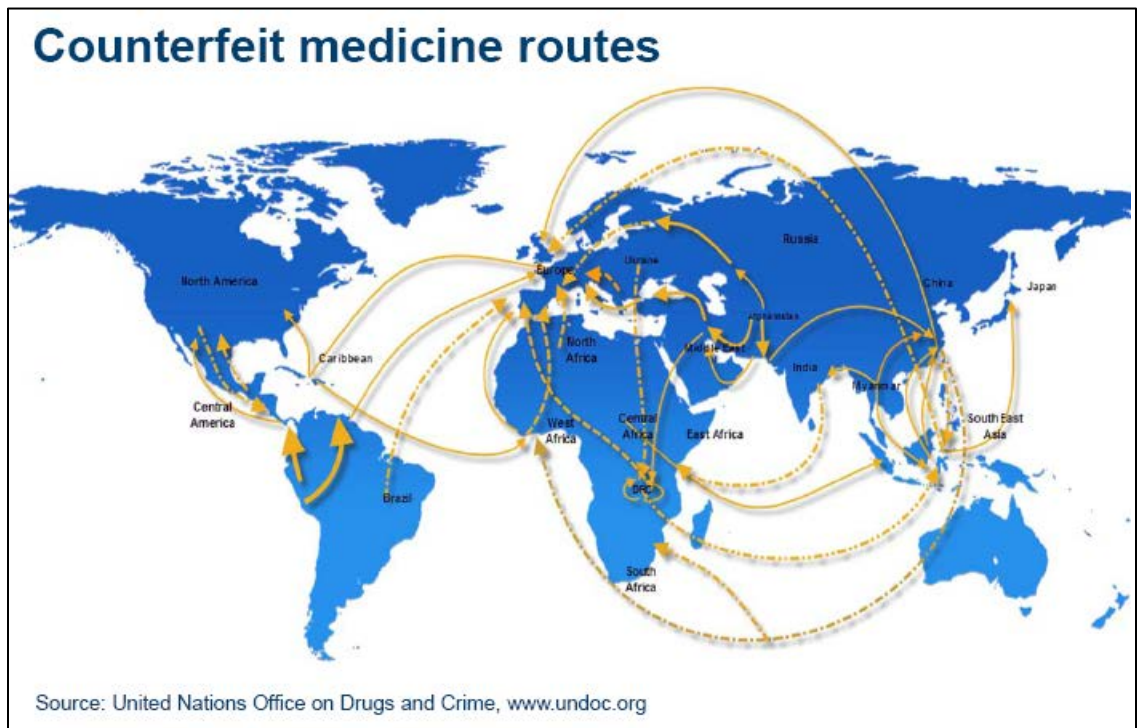


Figure 5: Counterfeit Medicines in the Global Supply Chain

According to the World Health Organization (WHO), counterfeit drugs have become lucrative business and attracted organized crime. Innovative modern technology has provided counterfeiters with advanced methods for duplicating products and packaging (WHO, 2010). It is estimated that globally, approximately \$75 billion was attributed in 2010 to counterfeit drug sales, an increase of 90 % from 2005 (Wiley-Blackwell, 2010).

The absence of or weak drug regulations contribute to growing counterfeiting, globally. According to WHO, out of 191 member states only 20% have a well-developed drug regulatory body; 50 % have some-sort of operational system, and the remaining 30% have either no drug regulation or very limited capacity to regulate manufacturers. These factors encourage counterfeiters because there is no penalty or repercussion for their actions.

Eyisi and Wertheimer (2012) identify other factors that fuel counterfeiting. First, individuals who are not aware of illicit products buy them because they do not know the problem exists and therefore, are not careful about what they buy. Second, criminals although they may have no pharmaceutical education, do have access to manufacturing systems by which they can imitate genuine drugs. Third, criminal organizations are becoming more interested in counterfeit drugs, driven by the enormous turnover and profit margins.

Weak supply chains and the internet create opportunities for intermediaries or middlemen to enter the supply chain and distribute drugs. This creates many opportunities for drug

counterfeiters to enter the distribution channel (Eyisi & Wertheimer, 2012). In recent times, the internet has become a major magnet for counterfeiters. According to WHO Internal Medical Products Anti-Counterfeiting Taskforce (IMPACT), approximately 50 % of drugs from internet sites are counterfeit (IMPACT, 2008).

According to the FDA,

“An individual who receives a counterfeit drug may be at risk for a number of dangerous health consequences. Patients may experience unexpected side effects, allergic reactions, or a worsening of their medical condition. A number of counterfeit products do not contain any active ingredients, and instead contain inert substances, which do not provide the patient any treatment benefit. Counterfeit drugs may also contain incorrect ingredients, improper dosages of the correct ingredients, or they may contain hazardous ingredients (FDA, 2014).”

Individuals taking counterfeit medicines are usually not aware of the health risks. There are many pathways through which a consumer may purchase drugs whether it is over the internet or over-the-counter. Regulatory agency may actively work to secure the pharmaceutical supply chain; but weak regulations, cheap drugs, and human element plague the supply chain with unsafe and effective drugs.

2.4 Drug Counterfeiting Statistics

According to WHO, counterfeits make up approximately 10 % of the global drug market and appear in both industrialized and developing countries. Perhaps, 25 % of drugs consumed in poor countries are counterfeit or substandard and annual revenues obtained in from these sales amounts to roughly US\$ 32 billion (<http://www.who.int/mediacentre/factsheets/2003/fs275/en>). Chakrabarti (2003) provides a list of counterfeit statistics from 1982 to present, and indicated the need for proactive approaches for preventing and reducing counterfeiting (see Table 1).

Table 1 : Counterfeit Events by Year

Year	Counterfeit Event Description
1982-1997	“Between 1982 and 1997, there were 751 cases reported of counterfeit drugs found in at least 28 countries. In 25 % of the cases, the drugs were reported to come from industrialized countries, 65% from developing countries, and 10% from unspecified sources (WHO press release, November 1997).”
1995	“In 1995, 89 people died in Haiti after ingesting cough syrup manufactured with diethylene glycol (a chemical commonly used as anti-freeze). This particular product was made in China and transported through a Dutch company to Germany, before winding up on the Haitian market (Sanofi-Aventis)”.
1999-2000	“According to WHO, between January 1999 and October 2000, they received 46 incident reports from 20 countries, 60 % of which were from developing countries (IFPW Focus, June, 2002).”
2000-2001	“42 reports of counterfeits from 20 countries during 2000 and 2001 (WHO, 2002) or 46 reports from 20 countries 60 % of which came from developing countries (IFPW Focus, June 2002).”
2001	“According to WHO, 5-8% of the worldwide trade in pharmaceutical is counterfeit (Security Management, 9/1/01).”
2006	Liang (2006) stated that the FDA “estimates that ~1% or less of drugs in the United States are tainted or counterfeited. Assuming only one tenth of one percent of drugs in the US are affected...more than 3.5 million to 350 million US prescriptions may be potentially affected by counterfeit drugs each year.”
2006	“In 2006, an unlicensed Chinese chemical plant sold a cheap poisonous counterfeit ingredient, diethylene glycol, which was mixed into cold medicine. It was later shipped to Panama, killing hundreds of people and disabling dozens more. The deadly drugs were traced back to a handful of Chinese companies that made and exported the poison as 99.5% pure glycerin (http://blog.opsecsecurity.com/recent-major-cases-of-counterfeit-pharmaceuticals/).”
2010	According to WHO (2010), “over 50% of cases, medicines purchased over the internet from illegal sites that conceal their physical address have been found to be counterfeit.” (http://www.who.int/mediacentre/factsheets/fs275/en/).
2010	The National Association Board of Pharmacy (NABP) estimated 1-2% of drugs in North America are fraudulent (NABP,2010).
2010	According to NABP (2010), “counterfeit sales are increasing at nearly twice the pace of legitimate pharmaceutical sales- estimated at 13% annually by the Center for Medicine and Public Interest.”
2012	In February, 2012, Roche a subsidiary of Genetech stated that counterfeit copies Avastin (cancer drug) which do not contain any active ingredient entered the US Supply Chain (http://www.securingpharma.com).

Bernstein and Shuren (2006) emphasized that there is no direct quantitative evidence to characterize the scope of counterfeiting in the US–PSC and attribute this to counterfeiters’ abilities to replicate the genuine products well. The current outlook on counterfeit drugs in the US-PSC is not promising. However, from counterfeit seizures data, there is a consistent upward trend of counterfeit drugs entering the legitimate supply chain as discussed in Chapter 1. Furthermore, the true extent of counterfeiting globally is unknown because there is no accurate or adequate source of data to quantify the problems as countries are not keeping records or reporting incidences of drug counterfeiting (Obi-Eyisi & Wertheimer, 2012).

2.5 Public Health Risk

There are many risks associated with taking counterfeit drugs. Consumers may not get appropriate therapeutic benefits or may experience adverse effects (Reggie, 2007; Newton et al, 2010). Newton et al (2010) provides a list of impacts:

- Increase mortality and morbidity;
- Engendering of drug resistance and loss of medicine efficacy;
- Loss of confidence in health systems and health workers;
- Economic loss for patients, their families, health systems, and the producers and traders in good-quality medicines;
- Adverse effect from incorrect active ingredients;
- Waste of enormous human effort and financial outlay in development of medicines, optimizing dosage, carrying out clinical trials, discussing policy change, and manufacturing medicines; and

- Increased burden for health workers, medicine regulatory authorities, customs officials and police offices.

2.5 Economic Impact

The Pharmaceutical Security Institute (PSI) estimated the size of the counterfeit drug market ranges from approximately \$ 75 billion to \$ 200 billion per year. PSI also estimated 800 fake versions of pharmaceutical products were manufactured around the globe in just 2009 (USA Today, 2010). Wertheimer and Norris (2009) explored the effect of counterfeit drugs on the macro-economy of a country. They stated that if the direct cost of therapies required in the treatment of communicable and non-communicable diseases is equal that of an undersea earthquake, then the indirect cost to society in the developing world due to counterfeiting infiltration is similar to an oncoming tsunami of unanticipated financial obligations and unfunded liabilities.

The economic cost of counterfeit in general affect countries in a number of ways. First, industries have direct competition with counterfeiters by loss in sales. Second, counterfeiting sometimes prevent entry of producers with genuine products. Third, consumers are deceived by believing they bought a genuine product and sometimes blames the manufacturer when the product fails, creating a loss of goodwill. Furthermore, the loss of goodwill threatens companies that want their brands associated with quality and exclusivity. Fifth, countries suffer because foreign producers with reputable brand are reluctant to manufacture their products where counterfeiting is high because they cannot rely on the legal system. This results in loss of investment and new know-how

from foreign products (OECD, 1998). The economic impact can result in loss of sales for companies and tax revenue for governments (OECD, 2007). Furthermore, if products from countries gain a reputation of being counterfeited, this may decrease export and perhaps lead to job losses and loss of foreign exchange (OECD, 1998).

2.6 The Pharmaceutical Supply Chain

The Kaiser Foundation defines the pharmaceutical supply chain as “....means through which prescription medicines are delivered to patients. Pharmaceuticals originated in manufacturing sites are transferred to wholesale distributors; stocked at retail, mail-order, and other types of pharmacies; subject to price negotiations and processed through quality and utilization management screens by pharmacy benefit management companies (Pumas); dispensed by pharmacies; and ultimately delivered to and taken by patients.”

The Institute of Logistics describes the pharmaceutical supply chain as “...the sourcing of active and inactive ingredients for approved products. Dosages are formulated and packed into various configurations. Products flow through company warehouses, wholesale distributors, retail pharmacies, medical institutions, and finally to consumers...”

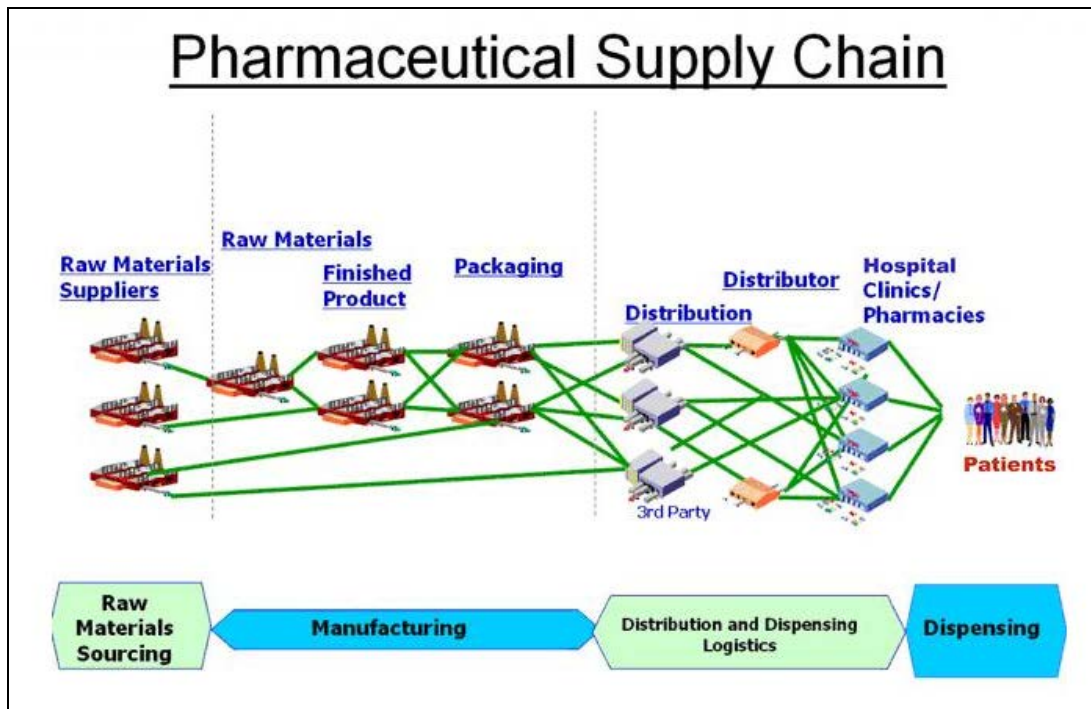


Figure 6 : Pharmaceutical Supply Chain
 (<http://www.rxresponse.org/about/Pages/NormSupplySys.aspx>)

The pharmaceutical supply chain (PSC) comprises of raw material suppliers, active pharmaceutical ingredients producers, finished dosage manufacturers, packagers, wholesalers, distributors, clinics, pharmacies, and finally, patients (Figure 6).

Raw materials are active pharmaceutical ingredients (APIs) and excipients. International Conference on Harmonization (ICH) ICH Q7A defined “active pharmaceutical ingredients” (API) as:

“any substance or mixture of substances intended to be used in the manufacture of a drug product and that, when used in the production of a drug, becomes an active ingredient in the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment of prevention of disease or to affect the structure and function of the body.”

API's are crucial for formulation of medicines product, hence, it is an essential element for the manufacturing of the final drug product (FDP).

United States Pharmacopeia (USP) defines "excipients" as:

“components of a finished drug product other than the active pharmaceutical ingredient (API) and are added during formulation for a specific purpose. Although listed as inactive ingredients by FDA, excipients generally have well-defined functions in a drug product. As with active ingredients, they may be small molecule or complex and may vary in terms of degree of characterization. They may be chemically synthesized or may be either natural source or biotechnology-derived (recombinant). In contrast to active ingredients, minor components of an excipient may have significant impact on its pharmaceutical performance. Depending on the intended use, an excipient in a drug product may be an active ingredient in another drug product.”

Finished dosage manufacturers (FDM) utilize the API and excipient components to produce a final product. At this stage in the supply chain, the FDM deliver products to licensed wholesale distributors, who then deliver products to pharmacies or hospitals. This flow of products from the FDM side was the status quo in earlier times; nowadays, this model is quite different. Globalization has shifted traditional pharmaceutical business models.

The distribution model today is different because primary wholesalers distribute to secondary wholesalers or to repackagers. Additionally, secondary wholesalers distribute to hospitals or pharmacies and repackagers (Enyinda et al, 2009). “The secondary distribution channel is the movement of products purchased from an authorized distributor, or source other than the manufacturer, to another intermediary. These products are then sold to the healthcare provider or the end user.”

The secondary distribution channel represents one method for the infiltration of counterfeit or otherwise adulterated drugs into the legitimate supply chain. Within the secondary distribution channel, drugs often change hands many times before reaching the provider or the end user.

The FDA regulates finished dosage manufacturers (FDM); however, the wholesalers receive a license from state boards of pharmacy (BOPs) and state department of health and BOPs enforces other regulations. The Drug Enforcement Administration (DEA) is responsible for regulating the supply chain for manufacturing, wholesale, prescription and pharmacies that handle controlled substances (e.g. narcotics) (Zimmerman, 2006). Zimmerman stated that problems of counterfeit arise when wholesalers do not hold a DEA registration. This creates a supply chain risk in that no authority (federal or state) may ever inspect the wholesaler. Counterfeit cases in the past have entered the legitimate supply chain because of this factor.

2.7 Drug Counterfeit Attributes

Sodipo (1997) provides a list of attributes for drug counterfeiting that was a part of broader research from the TRIPS (Agreement on Trade Related Aspects of Intellectual Property Rights) agreement.

These attributes include:

- Profit
- Cheap to Copy
- Easy to Copy
- Unsatisfied market demands
- Difficulties of detection and proof
- Non-deterrent laws and lacunae in laws
- Poor government policies
- Location of countries- production

The Organization for Economic Co-Operation (OECD) published a report on drivers for counterfeit and pirate activities in 2007. In this report, OECD grouped the driving factors by the categories: market characteristics, product characteristics, product, distribution, and technology, consumer characteristics, and institutional characteristics. Each category is decomposed to provide the supply and demand drives, see Table 2 (OECD, 2007):

Table 2: Driving Factors

Supply Chain Characteristics	Demand Characteristics
Market Characteristics	Product Characteristics
High Unit Profitability Large potential market size Genuine brand power	Low Prices Acceptable perceived quality Ability to conceal status
Product, Distribution, and Technology	Consumer Characteristics
Moderate need for investments Moderate technology requirements Unproblematic distribution sales High ability to conceal operations Easy to deceive consumers	No Health concerns No Safety concerns Personal budget constraints Low regard for IPR
Institutional Characteristics	Institutional Characteristics
Low risk of discovery Legal and regulatory framework Weak Enforcement Non-deterrent penalties	Low risk of discovery and prosecution Weak or no penalties Availability and ease of acquisition Socio-economic factors

Although the driving factors are presented from both a supply and demand perspectives; the decisions of what to produce and what markets to target are driven by market characteristics, technological and logical consideration, and institutions. Specifically, market potential can be coupled to market characteristics; market exploitation can be coupled to production, distribution, and technology; and lastly, market risk to institutional characteristics (OECD, 2007).

2.7.1 Market Characteristics

Market characteristics comprise of unit profitability, market size, and brand power. One of the driving forces behind counterfeiting is size of the market tied to unit profitability. The higher the potential for unit profitability, the higher the incentive for the product to be counterfeited. Unit profitability is determined by the cost of producing the product relative to price of product (Staake & Fleish, 2010 & OECD, 2007).

The market size is also an essential component of market characteristics. The larger the market size for a product (e.g., pharmaceutical product), the larger the profitability for counterfeiters. For example, larger customers based are tied to larger customer base for infringing goods (Wertheimer & Wang, 2012 & OECD, 2007).

Branded product is highly correlated to profitability and market size. For example, the popular brand name drug Lipitor used to treat cholesterol offers a high unit of profitability; and has a higher risk of counterfeiting. Brand name products or drugs may be more profitable relative to generic products and have a higher price premium due to the market size (OECD, 2007).

2.7.2 Production, Logistics, and Technology

With access to modern production facilities, counterfeiters are greatly reaping the benefits of producing fake products and raking in high profits (Staake & Fleish, 2010). For counterfeiter to enter the market, the technology and production capacity must be feasible. Counterfeiters frequently use known tactics from established bootlegging and

drug-trafficking organizations to bypass customs and countries that, conduct few inspections and have not been a significant source of counterfeit production. By doing this, they avoid being on the radar of customs officials. In addition, for countries where the intellectual property rights are strictly enforced, the postal services become the popular distribution channel.

2.7.3 Institutional Characteristics

The World Health Organization (WHO) stated that only 30 % of their members have laws and regulation to effectively combat counterfeit drugs (WHO, 2011). With limited resources for enforcement activities, the value of laws and regulations for the rights holder is diminished (OECD, 2007). The lack of or absent of a strong and structured regulatory system results in criminals producing counterfeits product at alarming rates.

This creates a permeable drug supply chain, counterfeits drugs go undetected, and drug counterfeiters escape with little or no punishment (Wertheimer & Wang, 2012). From the counterfeiter's perspective, the main concern is the ability to conceal operations. If the consequences or penalties are small, then the risk of discovery may have little significance to the counterfeiters.

2.8 Related Works

Spink (2009) presented a framework to determine product risk ranking that is built on five pillars: counterfeit-history; counterfeit ability; counterfeit-attractiveness; counterfeit-hurdles; and market-profile. His framework utilized the vetted factors discussed in OECD work done in 2007 (Spink, 2009). He presented a methodology to determine the product risk rank utilizing the five pillars with sub-risk factors discussed in the sections above. In addition, his model covers both the demand and supply factors and utilized qualitative/subjective approach for quantifying the product risk. His approach does not address factors that are highly correlated nor discuss the factors importance. Secondly, from a resource perspective, his model does not provide risk-stratification level; therefore his approach can become problematic when large sets of products are analyzed.

The Food and Drug Administration (FDA, 2013) published a comprehensive list of attributes to target potential counterfeit drugs:

- Drugs history of counterfeiting
- Drugs Price
- Drugs Volume
- Drug Dosage form
- Drug Clinical Use; and
- Whether similar products had a history of being counterfeited.

It is important to note that the FDA and OECD provide us with a comprehensive list of factors to consider when thinking about product counterfeit risk, however, no consensus on how to implement these criteria.

Trent & Moyer (2013) presented a qualitative risk assessment framework for determining the risk of product counterfeiting. Their perspective includes questions that are tied to severity and likelihood. For example, questions pertaining to severity include:

- Who will use the product?
- What is the intended duration of uses for the product?
- Will the product be implanted, infused, injected, or ingested?
- Will a health care professional administer the product or will the patient use the product himself/herself?
- What would happen if a product with no therapeutic benefit or active ingredient were used?
- Does the product require special handling such as special temperature or humidity controls?

For revenue and brand reputation from counterfeiters, questions include:

- What is the annual revenue for the product or where in your portfolio of products does this product fit in terms of revenue?
- Is this product a flagship brand for the company?

For likelihood of counterfeiting, questions include:

- Have there been any previous incidents of confirmed or suspected counterfeiting ...of the product?

- If the product is still in development and no market history is available, have similar or competitor products ever been targeted by counterfeiters?
- Have counterfeits actively been looked for in the marketplace or on the internet?
- Have market surveys been conducted or targeted buyers in high risk regions or from suspicious retailers?
- Has the customer complaint history been checked for potential counterfeit...product?
- Are there branded competitors in the marketplace or is the product the only one in its class?
- If there are competitors, where does the product fit in terms of market share and pricing?

While these questions are extremely useful for conducting individual product risk assessments, it should be noted that it could be coupled with the supply characteristics risk factors to distill down to meaningful attributes for analysis.

2.9 Counterfeiting in Other Industries

2.9.1 Perfume Industry

Most of counterfeit products are sold on the grey market through street traders and smaller shops at affordable prices. Consumers are not aware they are fakes and the product is lower quality. Oftentimes, traders present that the goods are stolen to deceive consumers that they are real. Three types of counterfeits perfumes: reasonable packaging, look-alikes but not identical, and fakes claiming false origin. Industry estimated 1 to 2 percent of their annual revenue is spent combating the illicit trade (OECD, 1998).

2.9.2 Aircraft Industry

The aerospace sector experienced a growth of counterfeit parts, specifically, aerospace electronics. The industry in 2005 experienced 3,300 incidents/occurrences and more than 8,000 incidents/occurrences in 2008 (AIA, 2011). These incidents may adversely affect the supply chain. Furthermore, effects may include:

- Government
 - National security or civilian safety issues
 - Cost of enforcements
 - Lost tax revenue due to illegals sales of counterfeit parts
- Industry
 - Costs to mitigate risk
 - Costs to replace failed parts
 - Lost sales
 - Lost brand value or damage to business image

- Consumers
 - Cost when products fail due to lower quality and reliability of counterfeit parts
 - Potential Safety Concerns.

Aerospace Industries Association (AIA) identified long life cycle, diminishing manufacturing sources, and material shortages as reasons for counterfeiting. For example, B-52 program went into service 1955 with an anticipated retirement date of 2040. Several changes occurred during the program life cycle; these include technologies for electronic components; design and support functions; software changes; and manufacturing process changes. Therefore, supporting these changes throughout their lifecycle requires parts that may no longer be available from the original manufacture. Thus, when parts are acquired from different distributor channels other than authorized original manufacturer-counterfeit parts may enter the legitimate supply chain.

2.10 Summary

Publications are limited on pharmaceutical counterfeit risk factors and their importance on drug counterfeiting. The few that are published provide us with a list of potential risk factors that experts will further evaluate for importance and applicability to drug counterfeiting. None of these published works has empirically explained the factors importance on drug counterfeiting or provided us with quantitative framework for prioritizing drugs at risk of counterfeiting.

Chapter 3: Counterfeit Attributes Selection and Analysis

3.1 Introduction

The business of pharmaceutical drug counterfeiting is lucrative but counterfeiters risk severe financial and legal penalties if caught. Counterfeiters survey the pharmaceutical drug supply chain to determine suitable point(s) to introduce adulterated products into the legitimate drug supply chain. As a result, regulators, representatives of pharmaceutical companies, drug manufactures, wholesale and retail drug suppliers and other legitimate stakeholders have a difficult task to prevent counterfeits from entering the legitimate drug supply chain.

Case studies and literature reviews were analyzed to determine the counterfeit attributes that provide a deep understanding of drug counterfeiting and are presumed good indicators of counterfeiting. Analysis identified ten attributes that are commonly mentioned in literature or evident in case studies as counterfeit indicators. These attributes are (1) country of origin (region), (2) product location, (3) product type, (4) product counterfeit history, (5) volume, (6) drug price, (7) drug shortage, (8) drug class, (9) medication class and (10) product complexity.

Figure 7 shows an overview of the work presented in this chapter. Following the identification of attributes from the literature and counterfeiting case studies, experts were asked to independently provide the attributes they believe are indicators of drug

counterfeiting. The attributes provided by Experts and those identified in the literature were consolidated and discussed in another round of elicitation with Experts.

During this discussion, Experts were asked to use their knowledge and experience of the pharmaceutical drug supply chain to provide input for the development of a conceptual model of the relationship between counterfeit attributes and their influence on counterfeiting. The resulting conceptual model, driven by both expert judgment and meta-analysis of the literature review, provides an explanation of the critical attributes that impact drug counterfeiting. In addition, Experts were asked to modify and validate the Counterfeit conceptual model. A discussion of each attribute and the Counterfeit conceptual model follows in Section 3.3 and 3.2, respectively.

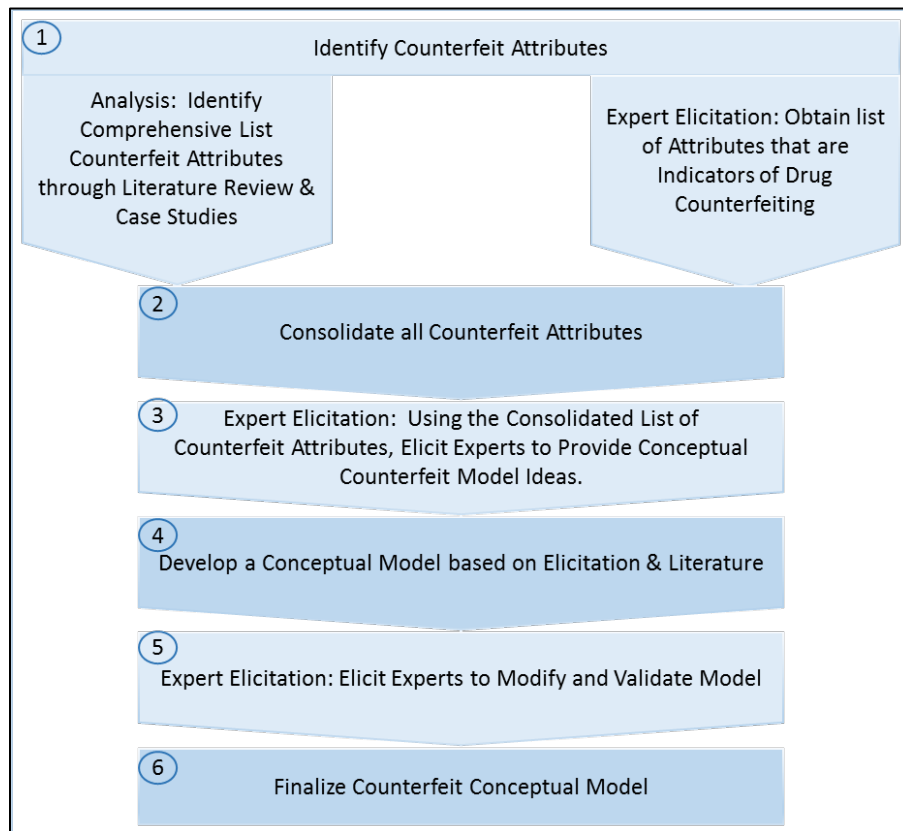


Figure 7: Research Flow

3.2 Counterfeit Attribute Identification and Expert Elicitations

Counterfeited products continue to surface within the legitimate drug supply. Regulators and the pharmaceutical industry use arguments of conjecture to determine the necessary course of action to try to mitigate counterfeits, rather than sound science and robust scientific tools and techniques. This is due, in part, to the vast landscape and limited knowledge of the pharmaceutical supply chain, and the limited published data in almost every aspect. As a result, expert elicitation (EE) is needed and utilized to supplement the knowledge gaps. According to Forrester (2005), expert elicitation is often used in scenarios that involve significant uncertainty and can have a significant effect on risk. Booker and Moyer (1990) discussed the benefits of EE. First, ideal for recognizing problem structured; and second, EE can be used to provide quantitative estimates.

3.2.1 Experts Definition and Experts

Several authors (Table 3) published studies indicating what qualifies an individual as an Expert. The U.S. Supreme Court in *Daubert vs. Dow Pharmaceuticals*, classifies legal experts in Federal Rule of Evidence 702 as individuals with scientific, technical, skill, experience, training, or education that will assist the trier of fact to understand the evidence or to determine a fact at issue (Penrod et al. 1995). Forrester (2005) determined the quality of expert performance in the field of medicine is based on the following attributes: peer nominations, certification, or specialized training in expertise, publication

expertise, as well as institution type, average level of formal education, event frequency, and average year of experience.

Table 3 : List of Expert Definition (Forrester, 2005)

Author/Reference	Definition
Weiss et al. 2003	Individuals who carry out a specified set of tasks expertly
Camerer and Johnson (1997)	Experienced predictors in a domain and have appropriate social or professional credentials
Cox (2002) and Lesgold et al (1988)	High-speed recognizers of abnormalities, and diagnostic classifiers who use a personal, organized, perceptual library linked into case-based knowledge.
<i>Daubert vs. Dow Pharmaceuticals</i> by Supreme Court	Individuals with scientific, technical, skill, experience, training, or education that will assist the trier of fact to understand the evidence or to determine a fact at issue.
Dreyfus and Dreyfus (1986, 1996)	The expert has high levels of procedural knowledge and skills (knowing how) as well as declarative knowledge (knowing what), and contextual flexibility (knowing when and where)

3.2.2 Expert Panel Size

The number of experts in the panel is still a widely discussed and researched problem today. Hogarth (1978) model suggested 6-10 experts is sufficient and Ashton and Ashton (1985) empirical work showed that between three and six experts lead to, high accuracy level and reported that using four experts reduced the error by an estimated 3.5%. Shirazi (2009) researched expert panel accuracy and determined that an expert panel of two improve the accuracy of estimates by 50% and selecting more than two experts improve the accuracy of estimates by more than 60 %. Their research further stated that increasing the expert panel from three to ten improved the results less than 10%. Libby and

Blashfield (1978) explained that increasing expert panel from 1 to 3 improves the accuracy of forecasting. They recommended an expert panel ranging 5 to 9.

3.2.3 Experts Selection

A total of eight experts were selected and interviewed to identify and validate the attributes that serve as good indicators of drug counterfeiting, along with their influences. Experts in this research were used for three primary reasons. First, to validate the factors identified from literature to determine their importance in being utilized in a decision model. Second, to add new factors that were not identified in literature. Third, to present an influence diagram showing the causal structure that could be used for qualitative validation.

In this research, experts were selected based on their years of experience and knowledge in the field of product development, manufacturing, and supply chain best practices (e.g., mitigating counterfeiting). Each expert had a minimum of five years of healthcare and pharmaceutical experience. They also had relevant knowledge of supply chain or product development. Furthermore, some of the selected experts conducted research in the area in drug development, and worked in brand protection. All experts had prior experience working on expert elicitation studies. Table 4 represents a summary of the qualification of the experts selected for this study.

Table 4: Expert Panel

Expert	Years of Experience	Degree(s)	Industry
1	13+	Regulatory Science, PhD	HealthCare
2	20 +	MPH, PhD	HealthCare
3	7 +	Regulatory Science, MBA	Pharmaceutical
4	10	Biochemistry, MPH	HealthCare
5	13	Molecular Biology, MS, MBA	Pharmaceutical
6	8 +	MS	HealthCare
7	16+	MD, PhD, MPH	HealthCare/Academia
8	30+	PhD	HealthCare/Academia

3.2.4 Elicitation Process

During the interviews, each expert was asked to validate identified counterfeit attributes as well as any new attribute that may enhance the understanding of drug counterfeiting. In addition, each expert was asked to describe his or her understanding of counterfeit drugs and how counterfeit drugs may affect consumers. They were also asked to provide a simple diagram or simply list the risk attributes and other factors that a supply chain risk manager (SCRM) would use for screening drug products at greatest risk of counterfeiting (see survey instrument in Appendix A). This approach is adapted from Kazemi (2011) dissertation research work.

After discussing risk factors with each individual experts, a conceptual (or influence diagram) counterfeit model was presented to them for their review and discussion. This phase of the survey process allowed experts to analyze the risk factors that were built from literature reviews and from one expert initially and provide their insights. Providing

a qualitative structure to experts allowed us to come to a consensus model after much discussions and revisions to the model.

The conceptual counterfeit model, shown in Figure 8, represents the culmination of all the conceptual models previously provided by experts, and review of literature. This model also resulted from a consensus among experts, following many discussions and revisions to the model. Parameters were deleted and added as well as influences were changed to reflect relationship from parent to child nodes.

Within an influence diagram, a parent node is closer to the root node on the same branch, while a child node is a step lower in hierarchy than the parent node on the same branch. For example, in Figure 8, the *Probability of Counterfeiting* is the root node, *Potential Product Shortages* is a parent node with *Material Shortages* and *Manufacturing Issues* being child nodes. Each expert was asked to rate this qualitative model on a scale from 0 to 100 for model accuracy and to validate the model for Completeness, Accuracy and Ease of Understanding.

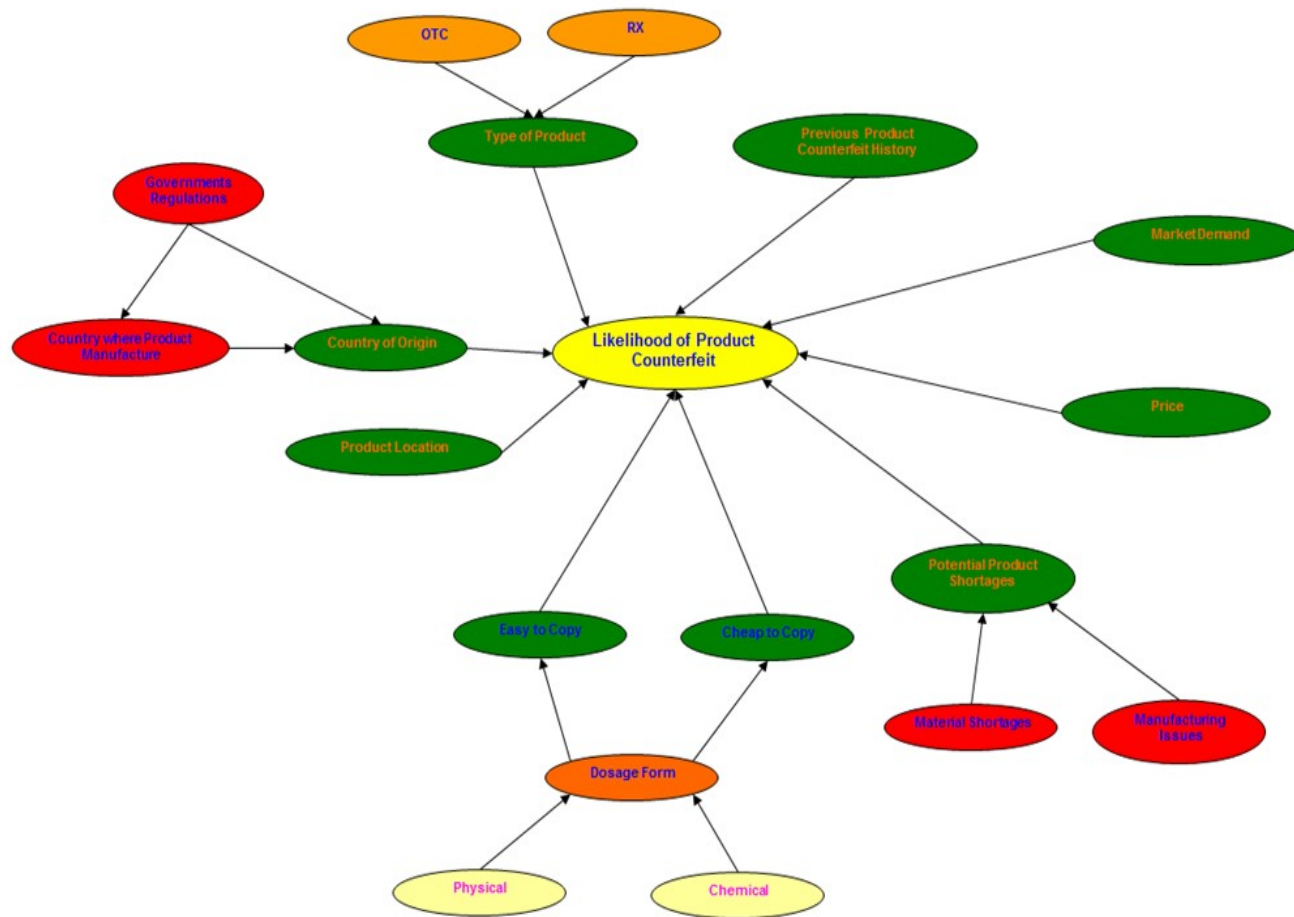


Figure 8 : Expert Model on Drug Counterfeiting

Completeness: The following questions were asked of each expert: From your perspective, to what extent does this model capture all important and relevant phenomena for the particular problem under study? On a scale 0 to 100, “0” corresponds to a model that does not include some important and relevant details, whereas “100” corresponds to a model that includes all the details that are considered important.

Accuracy: The following questions were asked of each expert: From your perspective, how accurately or realistically does the model depict important facts that predict the risk of pharmaceutical being counterfeited? On a scale from 0 to 100, “0” corresponds to a model that is unrealistic or inaccurate, while “100” corresponds to a model is realistic and accurate.

Ease of Understanding: The following questions were asked of each expert: From your perspective, how easy it is to understand the overall logic of the model? On a scale from 0 to 100, “0” corresponds to a model that is difficult to follow, while “100” corresponds to a model that is readily understandable.

Table 5 summarizes the responses of Experts to the three questions asked regarding completeness, accuracy, and ease of understanding. Of the eight experts elicited six responded.

Table 5: Expert Qualitative Validation of Counterfeit Factors and Concept Model

Expert	Completeness	Accuracy	Ease of Understanding
1	95	90	90
2	90	>80	90
3	80	85	90
4	90	85	90
5	90	90	90
6	90	>90	95

Experts agreed that the conceptual model presented is a good representation of causal network to detect the likelihood of product counterfeit and can be utilized for risk mitigation planning. They also added that no model is perfect which is reflected in their responses under completeness and accuracy; and that there is always uncertainty when modeling (see Figure 8). Each expert provided risk attributes that were unique to the model development. No single expert listed all the factors that were the most important; however, there were some overlaps between experts (i.e.: Expert I- Geographic and Cost; Expert II- Cost and Product Type).

3.3 Analysis of Counterfeit Attributes

3.3.1 Country of Origin (Region)

Experts unanimously agreed that country of origin for the final production of finished dosage form (FDF) products is of great importance to the probability of Counterfeiting. A report from the Pew Health Group (PEW, 2011) also supports this finding. The report states that “*geography and complexity of drug manufacturing have changed dramatically during recent decades, presenting new challenges to oversight and increasing risk that substandard drugs may reach patients.*” Manufacturing of pharmaceutical products is no longer within a country; it extends beyond country borders and now becoming a global system. Excipients can be manufactured in one country, the active ingredients in second country, and the FDF in a third country.

According to PEW, global revenues for pharmaceutical contract manufacturing is on the rise. The estimated revenues in 2009 for finished drug were approximately \$22.4 billion, and are projected to increase to \$39.6 billion in 2014 (see Figure 9). As the projection of foreign manufacturers increase, so does the risk of drug counterfeiting. This is especially true for developing countries that have weak regulatory systems, and loopholes in laws that address only spurious drugs rather counterfeit drugs (Obi-Eyisi & Wertheimer, 2012).

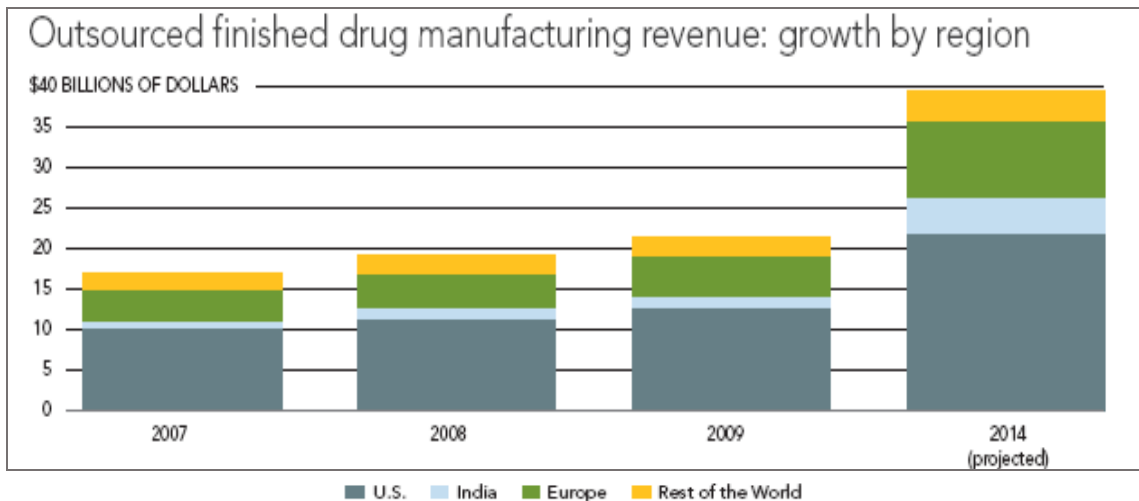


Figure 9 : Outsourced *Finished Dosage Form* Manufacturing Revenue: Growth by Region Worldwide (PEW, 2011)

Country of origin plays a critical role for screening and detection of potential counterfeit drugs in the US pharmaceutical supply chain (Reggie, 2007). Higher rates of counterfeit incidents are found in Asia, Latin American, and Europe (see Figure 10). Furthermore, the majority of drugs that are imported to the United States are from these countries that are experiencing high rates of counterfeit incidents (see Figure 11). Inadequate drug regulations, high corruption indexes, as well as lax penal sanctions are incentives for counterfeiters to enter the market to produce products that are potentially lethal to consumers. Counterfeiters represent both financially motivated criminal entities and terrorism groups. Criminals are in for the enormous turnover and huge profit margin and see counterfeiting business as a lucrative way to get a steady flow of money. For them it is less risk, high profits, and absurd penalties when compared with other criminal activities such as marketing narcotics (Obi-Eyisi & Wertheimer, 2012). Figure 12 depicts an influence diagram of the sub-factors of country of origin that increases the likelihood of drug counterfeits in the legitimate supply chain.

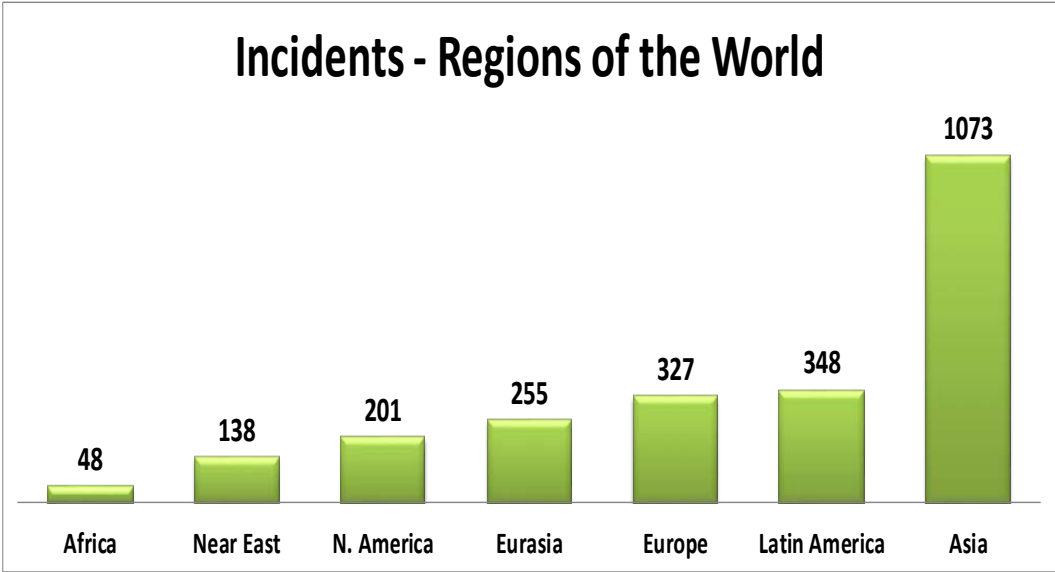


Figure 10 : Global Counterfeits Incidents (taken from PSI, 2012)

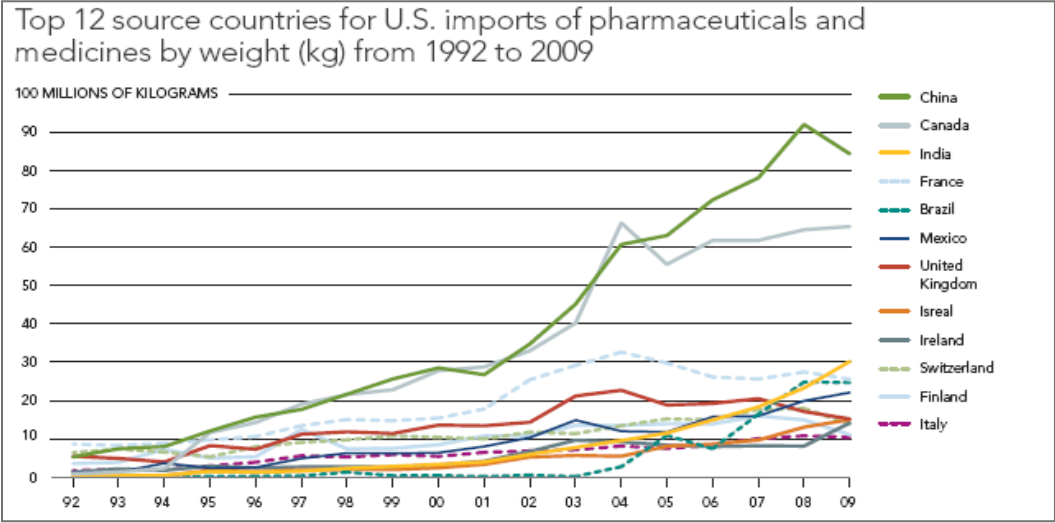


Figure 11: U.S Imports of Pharmaceutical Medicines

The lack of an official supply chain in developing countries and open markets present a huge risk not only to individuals who live within these countries but also consumers worldwide. No systematic structure for distributing drug allows intermediaries to become involved in the distribution of pharmaceutical products. This creates numerous opportunities to infiltrate the supply chain.

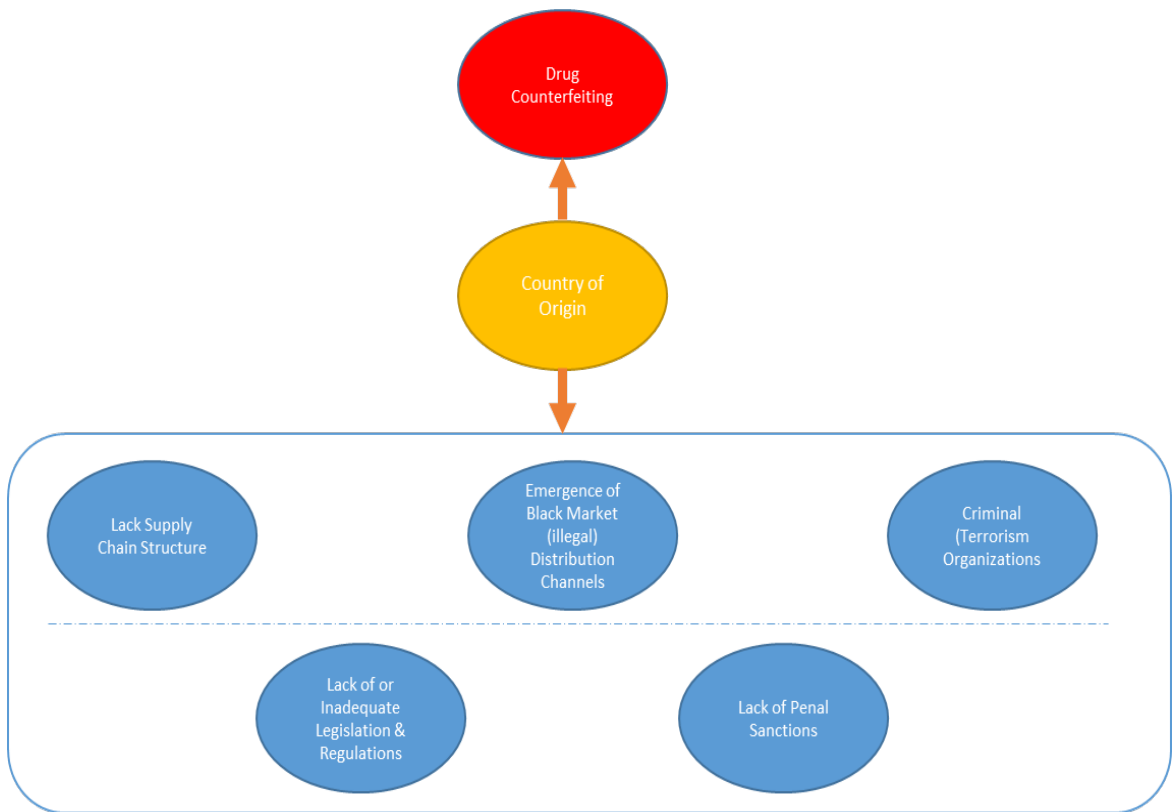


Figure 12 : Country of Origin Sub-Factors

3.3.2 Product Location

Product Location represents the locations that drug manufacturing and distribution progress within the pharmaceutical supply chain. Typically, the chain begins at the *raw materials sourcing* locations, then they move through the various types of *manufacturing* locations, and finally to the *distribution and dispensing* locations. The location of the drug product in the supply chain is critical in aiding decision makers in determining the likelihood of and how to identify possible counterfeit. Several domain experts interviewed in this research, and evidence in the literature affirmed that it is easier to distribute and access both prescription and over-the-counter (OTC) drugs over the internet. The vast and dynamic domain of the internet creates a challenging environment for regulators to find and prosecute drug counterfeiters, as well as to effectively educate consumers about counterfeiting risks. Counterfeits use the internet to market their illegal businesses of selling fake and bad drugs to consumers (Pfizer, 2012). According to Pfizer, the rise of counterfeits can be attributed to other factors such as under-regulated wholesalers and repackagers and the small penalties counterfeiters may face.

The business model of drug counterfeiters requires vigilance over all the major entities in the drug supply chain (see Figures 13 and 14). Drug counterfeiters infiltrate legitimate entities and fake drugs to now reach innocent consumers. There are varying degrees of counterfeit risks at the different drug outlets. Hospitals, online entities, clinics, and pharmacies are among the most common pharmaceutical drug outlets. Individual patients are most at risk of buying counterfeit drugs from internet retail outlets than private hospitals or clinics. Hospitals and clinics have protocols in place when purchasing drugs

from distributors or wholesalers; there is, however, a small likelihood that counterfeit drugs may end up at these locations.

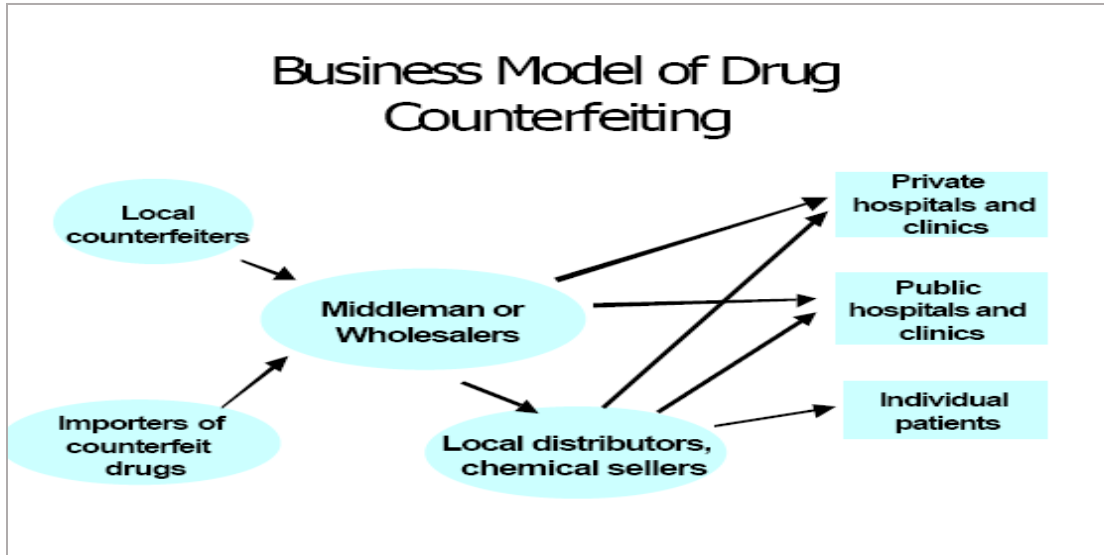


Figure 13: Business Model of Drug Counterfeiting (World Bank, 2005)

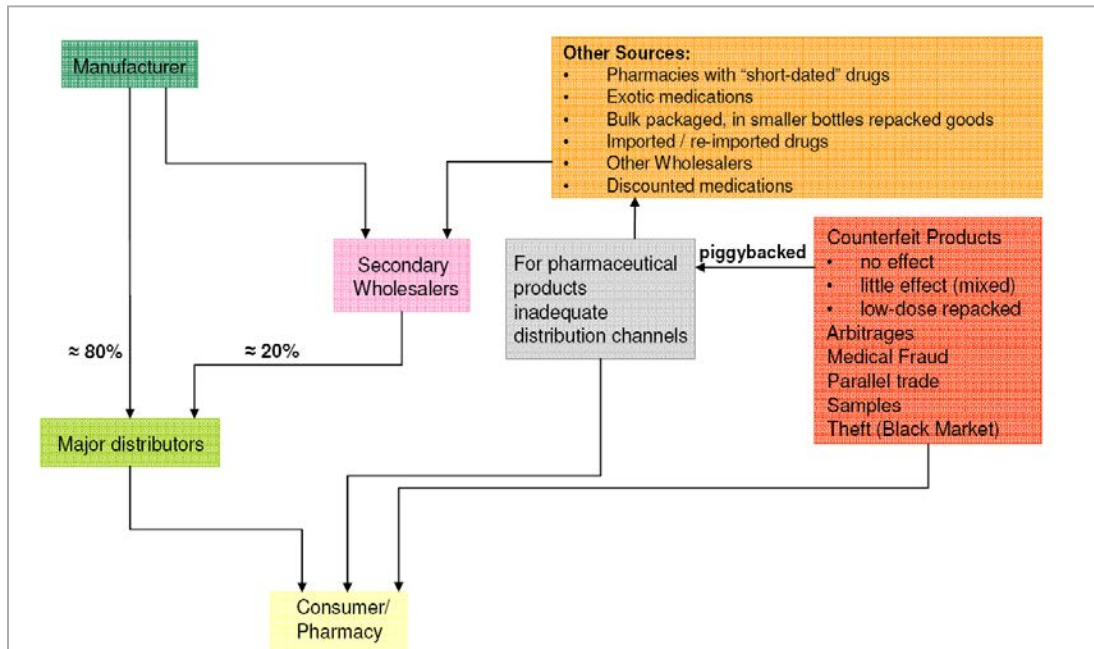


Figure 14 : Pathways in which a drug may reach consumer (Bridge, 2007)

The United States General Accountability (GAO) report on internet pharmacies discovered serious health risks associated with purchasing prescription drugs over the internet. There is sufficient evidence that location of product is important for screening and detection of potential counterfeit drugs. Table 6 summarizes a GAO study of 90 prescription drugs ordered and samples received from internet pharmacies. Of the 68 samples received, 45 were obtained without a prescription. Also, it should be noted that four of 68 samples were positively identified as counterfeits. Although the sample population is relatively small, 6% being counterfeited is still alarming, when considering the potential consequences of those adulterated drugs are considered.

Table 6 : Prescription Drugs Ordered and Received from Internet Pharmacies

Drug ordered	Orders placed^a	Drug samples received^b	Drug samples obtained without a prescription provided by the patient
Accutane	10	6 ^c	3
Celebrex	10	9	7
Clozaril	9	0	0
Combivir	6	5	1
Crixivan	6	6	2
Epogen	1	1	0
Humulin N	7	4	3
Lipitor	10	9	6
OxyContin	1	1	1
Percocet	0	0	0
Viagra	10	9	7
Vicodin/hydrocodone	10	9 ^{c,d}	9
Zoloft	10	9	6
Total	90	68	45

To strengthen the argument that location of product is important especially when the consumer population is easily exposed to buying bad drugs over the internet, GAO stated,

“Internet pharmacies pose challenges for regulators. State boards of pharmacy in many states have reported difficulty identifying Internet pharmacies located outside of their borders and have limited ability and authority to investigate and act against pharmacies that do not comply with state pharmacy laws when they are identified. In 2000, nearly half of the state boards had identified consumer complaints against Internet pharmacies or reported problems with Internet pharmacies not complying with state pharmacy laws.”

Table 7 depicts the issues and risk discovered from ordering prescription drugs over internet pharmacies.

Table 7: Observed Problems with Prescription Drugs Ordered (GAO, 2004)

Pharmacy Location	Canada	Other Foreign	U.S.
No pharmacy label with instructions for use (23 samples)		Accutane (3) Celebrex (3) Combivir (1) Crixivan (2) Humulin N (3) Lipitor (3) OxyContin (1) Viagra (2) Zoloft (3)	Celebrex (1) Zoloft (1)
No warning information (21 samples)	Celebrex (2) Zoloft (2)	Accutane (2) Celebrex (3) Crixivan (2) Lipitor (3) OxyContin (1) Viagra (2) Zoloft (2)	Lipitor (1) Zoloft (1)
Improperly shipped or dispensed (4 samples)		Humulin N (3)	Crixivan (1)
Unconventional packaging (6 samples)		Accutane (1) Celebrex (1) Crixivan (2) OxyContin (1) Viagra (1)	
Damaged packaging (5 samples)		Accutane (2) Celebrex (1) Crixivan (1) Lipitor (1)	
Not approved for U.S.	Accutane (3)	Accutane (2)	

Pharmacy Location	Canada	Other Foreign	U.S.
markets (35 samples)	Combivir (3) Crixivan (3) Humulin N (1) Lipitor (2) Viagra (1) Zoloft (3)	Celebrex (3) Combivir (1) Crixivan (1) Humulin N (3) Lipitor (3) OxyContin (1) Viagra (2) Zoloft (3)	
Counterfeit or otherwise not comparable to product ordered (4 samples)		Accutane (1) OxyContin (1) Viagra (2)	

3.3.3 Type of Product

Experts unanimously agreed that the *Type of Product* attribute is an important indicator of potential drug counterfeiting. High priced medicines such as anti-cancer and HIV drugs are some of the products at risk of being counterfeited because of the market demand (WHO, 2009). Counterfeiters are well aware of market demand and profitability of these drugs and are willing to enter the market to make a quick profit. Additional examples of counterfeit pharmaceutical drugs noted by the World Health Organization (WHO) are shown in Table 8. Liang (2006) mentioned that fake Lipitor and Viagra, two common drugs used to treat cholesterol and sexual dysfunction, respectively, are making their way from over the Mexican border to US yearly.

Table 8 : WHO Examples of Spurious/falsely-labeled/falsified/counterfeit (SFFC) Medicines

SFFC medicine	Country/Year	Report
Anti-diabetic traditional medicine (used to lower blood sugar)	China, 2009	Contained six times the normal dose of glibenclamide (two people died, nine people hospitalized) ¹
Metakelfin (antimalarial)	United Republic of Tanzania, 2009	Discovered in 40 pharmacies: lacked sufficient active ingredient ²
Viagra & Cialis (for erectile dysfunction)	Thailand, 2008	Smuggled into Thailand from an unknown source in an unknown country ³
Xenical (for fighting obesity)	United States of America, 2007	Contained no active ingredient and sold via Internet sites operated outside the USA ⁴
Zyprexa (for treating bipolar disorder and schizophrenia)	United Kingdom, 2007	Detected in the legal supply chain: lacked sufficient active ingredient ⁵
Lipitor (for lowering cholesterol)	United Kingdom, 2006	Detected in the legal supply chain: lacked sufficient active ingredient ⁶

In February of 2012, the Intercontinental Marketing Services (IMS) Institute published their top-line market data on top therapeutic classes by U.S. spending (see Figure 15). Commonly, counterfeited drug products such as lipid regulators, anti-diabetic and antipsychotic drugs are among the top grossing therapeutic classes of drugs in the United States.

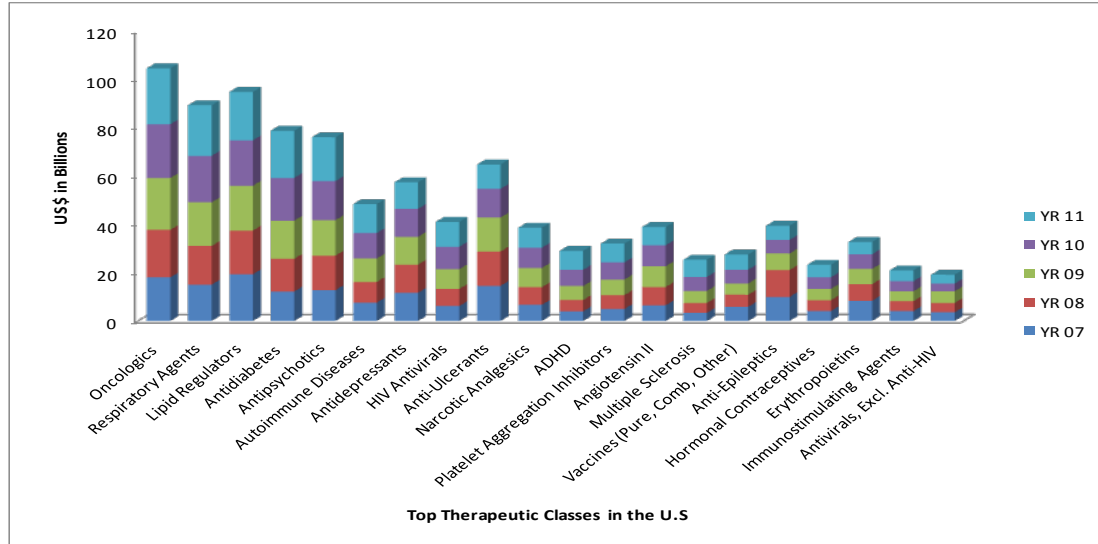


Figure 15 : Top Therapeutic Classes by U.S. Spending

It is worth mentioning that IMS did not publish information on OTC products; however, their information clearly depicted strong correlations between brand-name products and cost.

3.3.4 Product Counterfeit History

A pharmaceutical drug *product counterfeit history* is an important attribute for indicating the likelihood of counterfeiting. Experts agreed that previously counterfeited product is a strong indicator of risk of product counterfeiting- collectively stating that it is always important to do initial analysis to determine what has or has not been counterfeited is essential step in risk identification of pharmaceutical products. Several authors in the literature stress the importance of counterfeit history as a predictive factor for the likelihood of pharmaceutical counterfeiting (Spink, 2009; OECD, 2007). OECD (2007)

listed three steps in evaluating counterfeit magnitude and identification of goods that were counterfeited or pirated. Decision makers (DM) often encounter challenges with the availability of the resources needed to identify potential counterfeits in a given inventory. The incorporation of the *product counterfeit history* into the decision making process can aid in the identification of potential counterfeited drugs. There is one caveat to consider, when using this parameter as part of the decision-making process; products that have no previous counterfeit history do not necessarily indicate that they have lower risk of being counterfeited (Spink, 2009).

3.3.5 Market Demand

In order to understand the *market demand* for pharmaceutical drugs, it is important to know the market definition. Pindyck and Rubinfeld (2005) define the market as “*the collection of buyers and sellers that, through their actual or potential interactions, determine the price of a product or set of products.*” In the pharmaceutical products market, the buyers are the pharmacies, the hospitals, and the consumers, etc; the sellers are the big pharmaceutical companies, the primary and secondary wholesalers and a number of other entities. The market as a whole is more than an industry; it is a collection of firms that sells the same or similar products (Pindyck and Rubinfeld, 2005).

In the case of *market demand* from a product perspective, it is the demand for a particular product at a particular price that consumers are willing to pay.

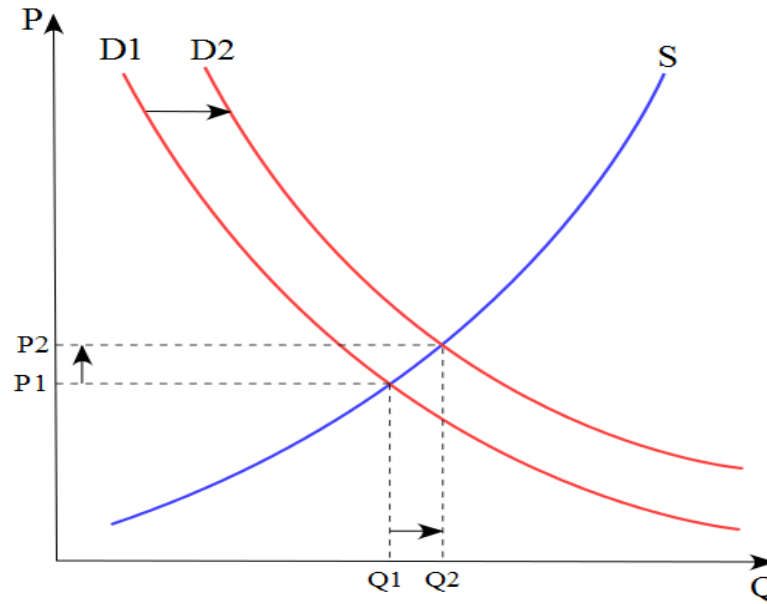


Figure 16 : Supply and Demand Curve (http://en.wikipedia.org/wiki/Supply_and_demand)

In the case of drug counterfeiting, the markets for some types of pharmaceutical products are dissatisfied (Spink, 2009). This environment of unfulfilled demand for products and potentially high profits, create opportunities for counterfeiters to enter the market to satisfy these demands. Experts agreed that market demand is a good indicator for a product's risk of counterfeiting. Specifically, experts discussed that this important characteristic when coupling to product unit cost and potential profitability. Counterfeiters typically target products that have high profits, larger market, and high demand.

The market demand for top brand name and patented drug products are extremely high as indicated in the IMS Health data (see Figure 17). Miller and Duggan (2010) listed alimentary, anti-infectives, cardiovascular, central nervous system and cytostatic drugs as

the top counterfeited products. Correlating their studies with IMS health data; they found that Lipitor, the number one block-buster cholesterol medication excels in sales volume and is listed as one of the top five most counterfeited drugs.

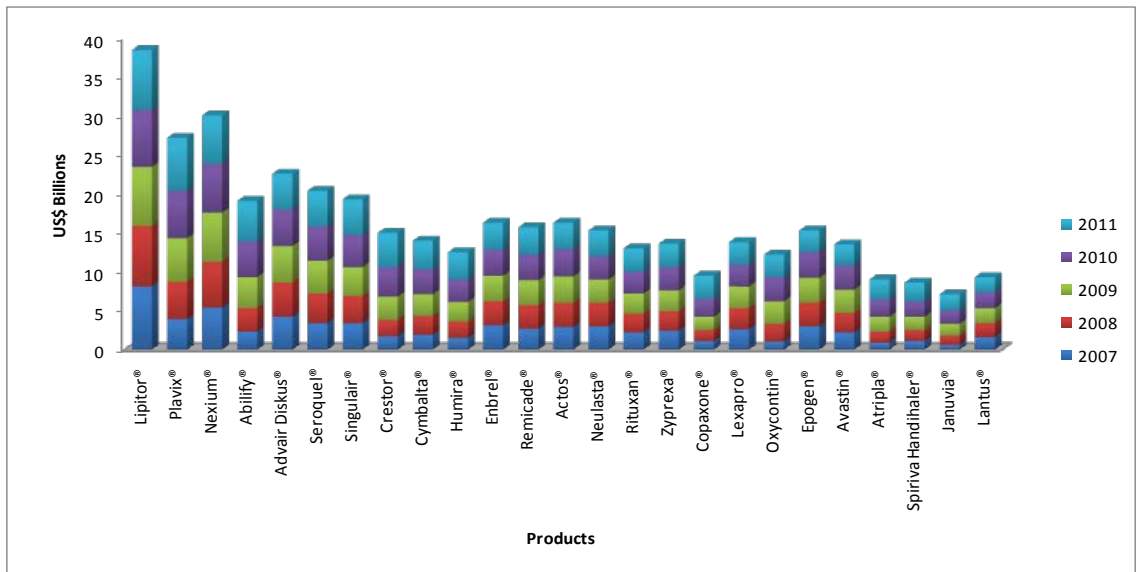


Figure 17 : Top U.S Pharmaceutical Products by Spending US\$ in Billions

While the demand for brand-name and patented drugs may be higher than that of generic drugs; it does not hinder counterfeiters from trying to enter the market. Inksure Technologies made the best possible case why generic products should be considered in the of risk model as do some of the experts in this research. Inksure stated the demand for generic drugs is increasing market share. He also emphasized that many of the popular brand-name drugs are about to reach their patent expiration date or have expired, thus creating new markets for manufacturers to make and sell. The estimated value of the generic market is projected to be around US\$ 168.7 billion according to Inksure. With these increases in both demands and profits, counterfeiters are strategically entering the generic market to capitalize on the demand.

3.3.6 Drug Price

Economic theory determines the price of product and the level of production at which marginal revenues equals marginal costs (OECD, 2008). Figure 18 depicts the scenario in which prices of genuine products are determined:

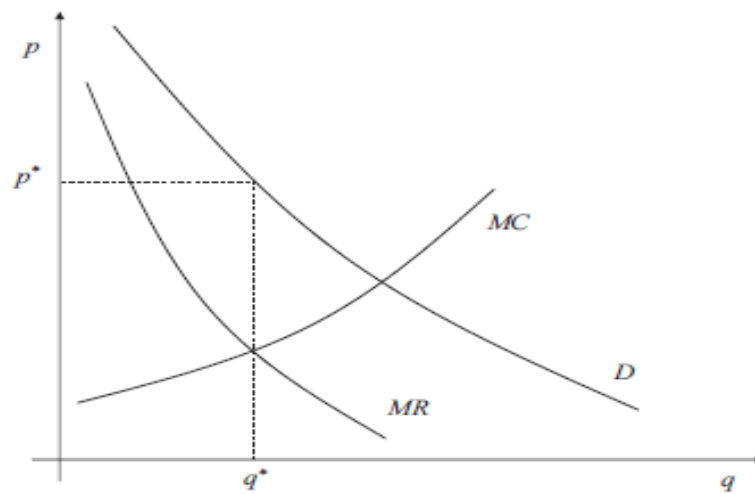


Figure 18 : Determining Price of Genuine Products (OECD, 2008)

Note (taken from OECD, 2008): Demand is depicted by a downward sloping curve denoted D . The price p^* is set where the marginal revenue equals the marginal cost ($MR=MC$) resulting in a market size q^* .

The *drug price* attribute will help supply chain managers (SCM's) determine which products are more at risk of being counterfeited. As mentioned previously, it is important to understand price setting concept because counterfeiters are competing with legitimate drug owners, especially in cases where the products are in high demand and there are large profit margins. Experts agreed that drug price is another important attribute to consider in the drug counterfeit model. Specifically, experts spoke about the high cost of

pharmaceutical drugs pertaining to price differentials. People will seek cheaper drugs if a market exists, especially unregulated markets. Spink (2009) and FDA (2013) presented in their studies that *drug price* is an important attribute for products at greater risk of being counterfeited. However, price, if measured alone is not a key indicator for predicting the risk of drug counterfeiting. A drug counterfeiter considers a number of factors when determining which drugs to counterfeit. For example, a drug with high demand and low cost is profitable to a counterfeiter after factoring in the volume concept along with price

3.3.7 Drug Shortage

According to the University of Utah Drug Information Service (UUDIS), an organization that partners with the American Society of Health System Pharmacists (ASHSP) to track nationwide drug shortages in the US, a *drug shortage* occurs when “total supply does not meet demand for a drug on a nationwide or regional basis for a period of time that necessitates changing the practice of treating the patient.” Some of the experts in this study believe drug shortage could be a useful attribute to include in the counterfeit model and stated it is useful to watch market trends for potential material shortage(s) that could impact the final product(s) for distribution. Previous studies identified earlier in this dissertation did not address the concept of product [drug] shortage as an attribute that helps SCM’s identify products at risk of counterfeiting. However, Bloomberg news (2013), stated:

“Shortages of some injectable cancer drugs have created an opening for dangerous unapproved versions of Roche Holding AG (ROG)’s Herceptin and Amgen Inc. (AMGN)’s Neupogen to be sold to clinics...”

Counterfeiting operations are very informed about product statistics and often try to capitalize on the market to sell their adulterated products during times of shortages caused by insufficient manufacturing output to meet the demand (Karalias, 2010). While product shortages are the realized event at the end of the supply chain; it can stem from many different sources upstream or downstream in the supply chain. According to the FDA (2011), the primary reasons for shortages were problems at the manufacturing facility (43%), delays in manufacturing or shipping (15%) and active pharmaceutical ingredient shortages (10%); and manufacturing quality problems such as findings of glass shards, metal filings, and fungal or other contamination in products.

Drug shortages may force providers to buy drugs from the gray market and from distribution channels that are not authorized by the manufacturer to distribute or sell their products. In the gray market, suppliers typically get small quantities of drugs that are in shortage and sell them at an inflated price. Oftentimes, it is difficult to determine the source of drug products in the gray market. As a result, the drug safety and efficacy can become compromised. Consumers may not get the therapeutic treatment from the drug, and as a result, may experience adverse events or receive poor outcome (GAO, 2011).

Information on drug shortages or the likelihood of product shortages can be found through several avenues such as the ASHP and the Food and Drug Administration (FDA). There are lists of drugs at risk of shortages as well as drugs that are currently in

shortage. In addition, this information is readily available to SCRM's to retrieve from both entities websites. SCRM's can quickly assess the risk of drug counterfeit through look-up of drug in questions.

3.3.8 Product Complexity

Product complexity signifies the ease at which a product can be cheaply manufactured or copied. Counterfeiters, like the legitimate manufacturers, are in the business to make a profit; therefore, they target products that are easy to copy and have low risk of detection. For example, counterfeiters are unlikely to attempt the counterfeiting of a biologic vaccine product. The process to make this and similar products require complex manufacturing techniques, very stable environments and logistic planning. This variable characterizes the product's technological and innovative requirements to manufacture and introduce the drug products into the legitimate supply chain. Experts agreed product complexity is a useful variable to measure if a product is at risk of counterfeiting. For example, one expert mentioned that it is difficult to counterfeit biological products because the process to manufacture them is highly complex as well as the cost to manufacture them is high.

Pharmaceutical Inspection Convention Pharmaceutical Inspection Co-Operation Scheme (PIC/S) is an organization comprised of several health regulatory authorities harmonized and defined the product complexity. PIC/S (2012) defined product complexity as the following:

- 1) In general, the greater the number of subcomponents that make up any one product package, the greater the risk to more product complexity. For example, a pack of an injectable product may have 4 components;
- 2) Products requiring special storage and distribution : (e.g., cold chain products, short-shelf products such as radiopharmaceuticals can be complex to manage)

Figure 19 illustrates the elements that supply chain risk managers (SCRMs) can use to determine product complexity. These elements include accounting for the ease to manufacturing the products, the technological needs to produce the products, distribution challenges, sales, and as well as, the ability of the product to remain undetected within the drug supply chain, and ability to conceal operations and easiness to deceive consumers (OECD, 2007a).

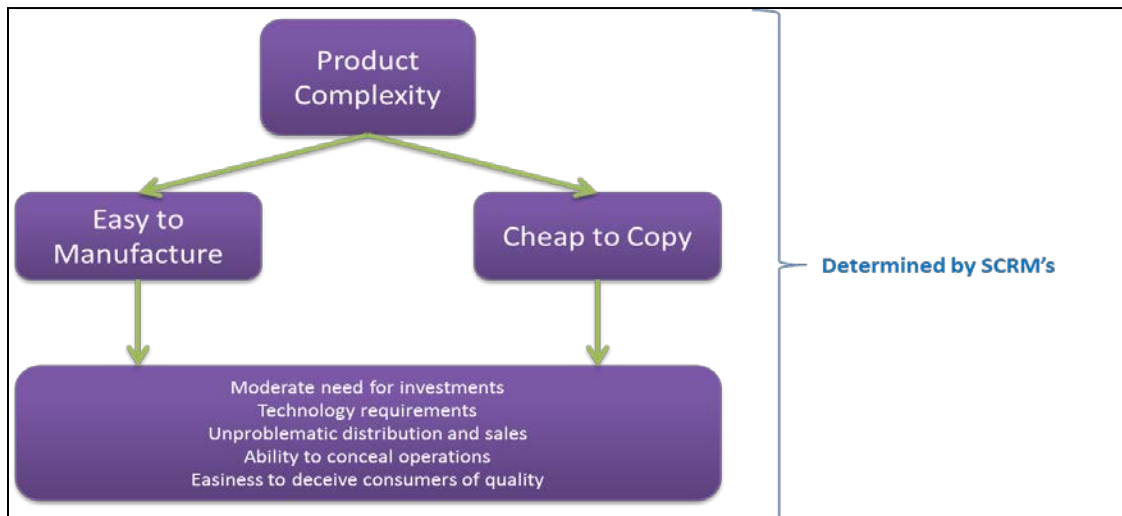


Figure 19 : SCRMs' guiding elements to determine product complexity

While most counterfeiters are not thinking about value (e.g., patient safety, public health risk), they do think about cost. Highly profitable products (e.g., oncology drugs), often require a higher level of planning and very complex logistics coordination.

3.4 Summary

In summary, through literature reviews, case studies, and expert elicitations we were able to identify critical counterfeit attributes that can be utilized in a decision model for drug prioritization pertaining to counterfeiting. In addition, we developed a conceptual model that be utilized to explain the relationship between the attributes and drug counterfeit. The conceptual model derived both from experts and literatures provide us with an initial framework for discussion and analysis and fit with other research conducted in product counterfeiting.

Chapter 4: Data Collection and Descriptive Analysis

4.1 Introduction

This chapter summarizes the data collection methodology and the descriptive statistics of the data collected from published case studies and literature.

4.2 Data Uncertainty

Gathering data on drug counterfeiting is limited. In order to do data analysis on the counterfeit attributes identified in this study, data had to be collected from publically available sources described in this chapter. Assumptions were made to gather data on the attributes units (e.g., average price per unit). Therefore, rounding, could introduce error into the analysis by taking averages. Thus, based on the assumptions, uncertainties could have been introduced into the analysis. Other sources of data uncertainties can arise from the following: (1) errors made during documenting information from the primary sources; (2) misinterpretation of the data; and (3) errors from published materials (Blair et al., 2013).

4.3 Data Collection

Information pertaining to drug counterfeiting is limited and scattered. Structured data for analysis is non-existent, and it is a sounding theme from literature and regulatory agencies around the globe. Structured data is considered information with a high degree of organization and defined fields (e.g., attribute names, data types etc.). Since structured data is not available, in this research, a data methodology was designed to create a

structured framework to collect meaningful data and do descriptive analysis. The process is depicted in Figure 20. First, literature reviews was conducted to determine a set of counterfeit attributes. Second, experts were used to validate the usefulness of these counterfeit attributes in a risk model (or decision model) as well as potential of new attributes to be included. Third, each attribute is defined and unit of measure is defined. For example, price of drug is measured by average unit cost in dollars and volume is measured in number of units sold. Fourth, data is collected and entered in structured format for analysis.

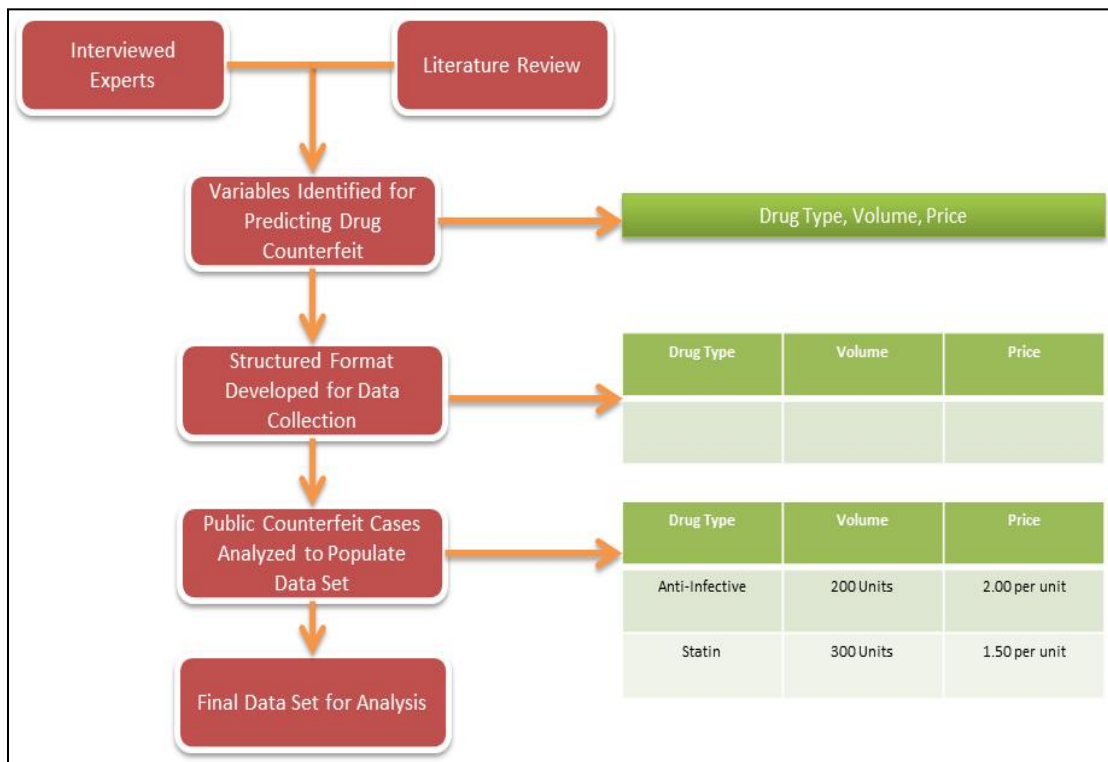


Figure 20 : Data-Methodology Process Flow

Several data sources were utilized to create the structured pharmaceutical counterfeit data analysis table. Published case studies, Counterfeit Drug Incidence Encyclopedia (CDIE), The Red Book, World Health Organization (WHO) and IMS Health provided relevant variable information that was utilized to form the foundation of the counterfeit dataset. Each data source provided different information on a specific counterfeit drug (see Table 4.1).

Published case studies consisted of publicly available information on drug counterfeiting. Information was extracted from government agencies publications (both United States and Foreign Regulatory Bodies), research journals, as well as Non-Profit Organizations (PEW and PSI), and the World Health Organization (WHO).

The Counterfeit Drug Incident Encyclopedia (CDIE) documents counterfeit incidents in the legitimate supply chain worldwide. CDIE provides high level analysis on incidents, for example, incident location, where in the legitimate supply chain the drug was discovered, country manufactured, type of drug(s), unit cost, number of people affected by taking the drug(s), and if a conviction was obtained.

Table 9: Data Sources and Variable Information

Case Studies	Counterfeit Incidence Encyclopedia	Red Book	IMS Health	WHO
Type of Drug Counterfeited, Quantity (if available), Location in the Supply Chain, Country Manufactured (if available), Country Discovered (if available), Previously Counterfeited, Drug Shortages (if available)	Type of Drug Counterfeited, Volume (if available), country discovered, country where manufactured, # individuals affected (if available), unit price (if available)	Product Name, Ingredient, Brand (Generic or Brand Name), Average Unit Price	Product Name, Total Units Sold	Types of Drug Counterfeited, Country of Origin

Table 10 : Attribute by Data Sources

Data Sources					
Attribute	Cased Studies	Counterfeit Incidence Encyclopedia	Red Book	IMS Health (Public Data)	WHO
Product Type	X	X	X	X	X
Volume	X			X	
Average Price			X	X	
Product Location	X	X			X
Product Complexity	X	X			
Product Shortage	X				
Previous Product Counterfeit	X	X			X
Region	X	X			X
Drug Class	X				X

The Red Book Online® is a database from the American Academy of Pediatrics (AAP) that provides information on drug manufacturers, drug active ingredients, whether a drug is a brand name or generic, packages size, as well as average package price and average unit price.

The Intercontinental Marketing Services (IMS) Health provides current pharmaceutical data on sales of the top 20 global products and therapeutic classes along with top therapeutic classes by U.S. spending and channel distribution by U.S. spending. World Health Organization (WHO) provides data on percentage of counterfeit by therapeutic categories, testing methods used (if available) for screening counterfeit as well as the distribution channel drug in which the counterfeit was discovered. The aggregation of the various data sources, published literature, and case studies allowed the collection of 134 data points that were used for analysis.

4.4 Descriptive Summary

The sample set for this research is comprised of 134 case analysis (N=134). As described in the data methodology section, these cases were collected from different sources and quantified for this research.

Through extensive research and expert interviews, 10 variables are selected to be utilized in this research (see Table 10). The previous section provided detail description on each variable, this section, depicts how they are transformed for analysis.

Table 11: Attributes Nomenclature

Variable	Variable Symbol
Medication Class	MC
Volume	VLM
Average Price	AVP
Product Type	PT
Drug Class	DC
Region	RG
Product Complexity	PC
Product Shortage	PS
Previous Product Counterfeit	PPC
Product Location (Discovered)	PL

The variables are coded to enable further analysis to be conducted, for example, there are numerous types of medication class; therefore, a nomenclature had to be developed to enable us to conveniently state the type of medication class we are analyzing. Furthermore, several assumptions had to be made to ensure the proper coding of information.

4.4.1 Medication Class

According to Bihari (2008), *a medication class* is a group of medications that may work in the same way, have a similar chemical structure, or are used to treat the same health condition. In this research, we group identified products according to their medication classification (e.g., Cialis and Viagra are grouped as Life Style). In a sample size of 134 (n), we discovered 20 different types of medication class. Table 11 shows the frequency distribution of counterfeit medicine by therapeutic class. From the analysis we discovered lifestyle drugs (~19%), anti-infection (~18%), statins (~10%), and analgesics drugs

(~7%) are drugs with the highest counterfeit rates. It is important to note that within a medication type, various drug products exist with different price points and consumer demand. In this research, we take products and characterize them by medication class.

Table 12: Descriptive Summary of Class of Counterfeit Medication

Medication Class	Frequency	Percent
ACE Inhibitor	5	3.73%
Analgesic	9	6.72%
Anticoagulant	1	0.75%
Anti-diabetics	2	1.49%
Anti-Infection	24	17.91%
Anti-Obesity	4	2.99%
Antipsychotic	3	2.24%
Anti-Viral	4	2.99%
Benzodiazepine	3	2.24%
Beta Blocker	4	2.99%
Birth-Control	1	0.75%
Hormones	3	2.24%
Life Style	26	19.40%
NSAID	4	2.99%
Oncology	8	5.97%
Proton Pump Inhibitor	1	0.75%
Statin	13	9.70%
Steroids	7	5.22%
Suppressants	4	2.99%
Vitamins	8	5.97%

4.4.2 Volume

The total number of units sold in the last two years measures the volume (VLM) variable. The volume distribution captures the numbers of units sold for each product identified in this analysis. Approximately 59 % of products were in the 250 thousand range and above (see Figure 21). This variable is surrogate to measure drug demand since there are no other measures to capture product demand in the market place.

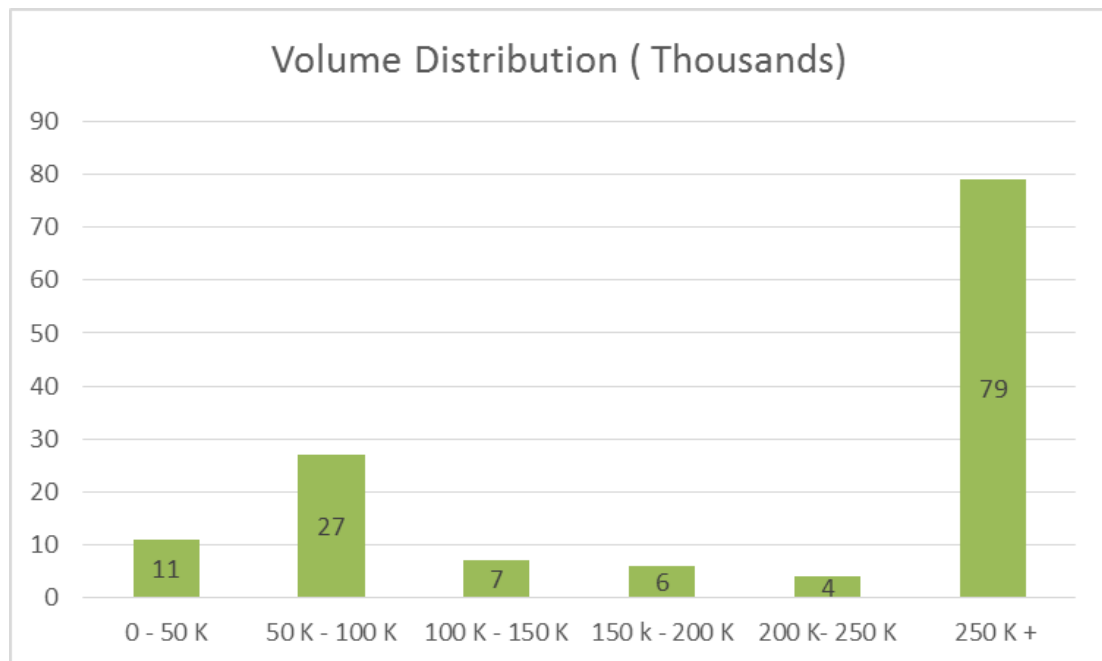


Figure 21: Counterfeit Drug Volume Distribution

4.4.3 Average Price

The *average price (AVP)* variable is derived from the sum of all the unique product types unit cost divided by the different combination of unique products available in the market. This enables us to get an estimate of price per unit of drug. Figure 22 depicts the ranges of prices for drugs that were counterfeited in the data set created.

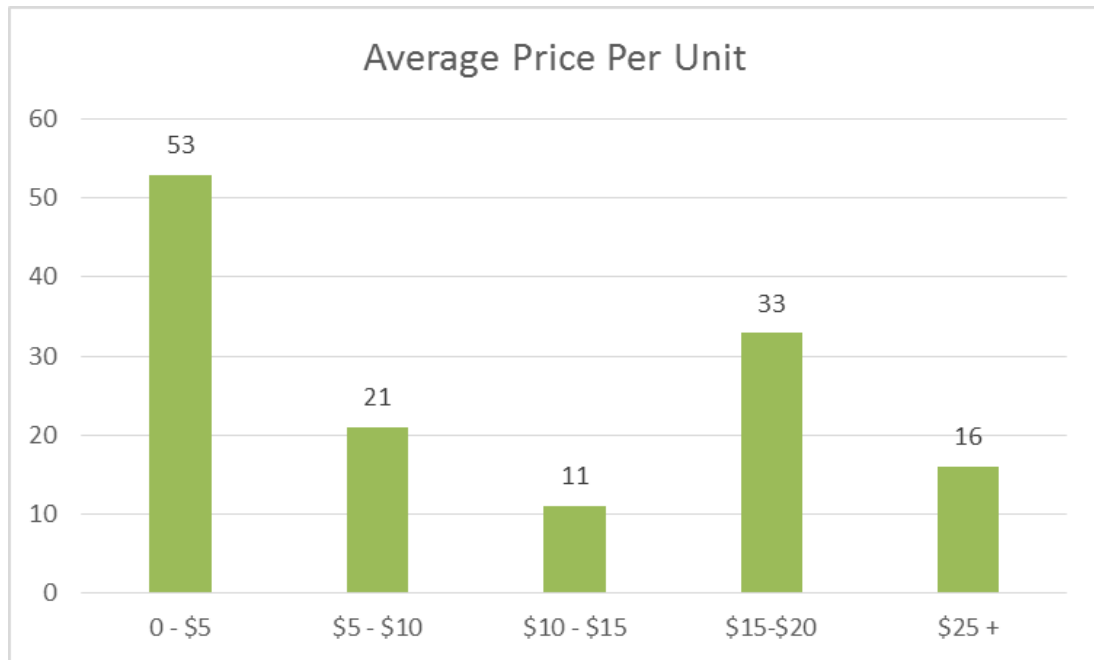


Figure 22: Average Price per Unit of Counterfeit Drug

4.4.4 Product Type

The *product type (TP)* variable is composed of two elements: brand and generic drug products. A brand-name drug product is marketed under a specific trade name by a pharmaceutical manufacturer; however, the pharmaceutical manufacturer is the sole source for the drug product. A generic drug product is made with the same active ingredient in the same dosage form as a brand-name product, however, it is sold under a

generic name and can be produced by multiple pharmaceutical manufacturers. In the data set, ~54% of the products counterfeited were brand name products and ~ 46% were generic products.

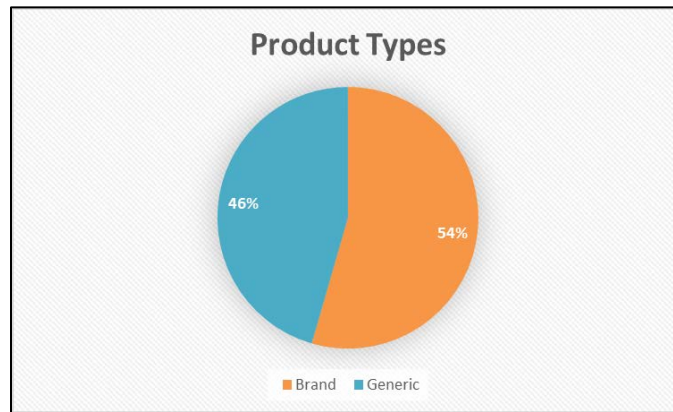


Figure 23: Product Types

4.4.5 Drug Class

The *drug class (DC)* variable is composed of two elements: prescription (Rx) and over-the-counter (OTC) drugs. OTC drugs may be sold directly to a consumer without a prescription from a healthcare professional, as compared to Rx drugs. Prescription products accounted for 90 percent of drugs counterfeited in the data set.

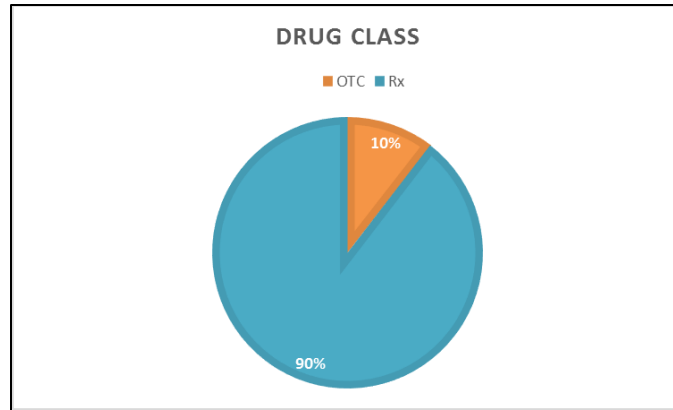


Figure 24: Drug Class Type

4.5.6 Region

The region (RG) variable is comprised of geographical locations: Africa, Asia, Central America, Europe, Middle East, North and South America. These geographic locations cover the landscape of drug manufacturers as well as areas from which counterfeit drug products can originate. Table 12, depicts the frequency or count of counterfeit drugs for each geographic location. It is important to understand that this represents the location of origin and not necessarily, where the product was manufactured and/or counterfeited. It is interesting to see that in the majority of cases there is an association/link with Asia as the majority of offshore pharmaceutical manufacturing is occurring in either China or India. As the pharmaceutical manufacturing arena becomes more global, it is expected that a lot of products introduced into the US pharmaceutical supply chain will originate from different locations around the globe. Geographic location is an extremely important element in the decision making framework. From the meta-analysis conducted, most of the cases that had counterfeit incidents occurred in developing countries.

Table 13 : Geographic Distribution

Region	Count
Asia	73
Europe	31
Africa	12
North America	7
Central America	5
South America	5
Middle East	1

4.4.7 Product Complexity

Product complexity (PC) is a derived variable from easy to manufacture, and cheap to copy concept. This variable characterizes the product technology and innovations required to manufacture and introduce the drug products into the pharmaceutical supply chain. Approximately 55% of the products were determined to be complex requiring technology, logistics planning, and shipping, which are not simple to execute (see Figure 25). The complexity was assessed using an expert in the field of drug manufacturing.

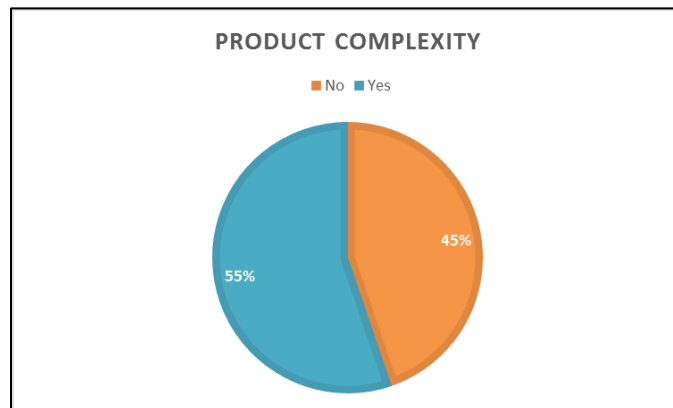


Figure 25: Product Complexity

4.4.8 Product Shortage

Product shortage (PS) attribute is introduced into the decision making model due to counterfeit events that have occurred in the past several years. Product shortages occurs when demand exceed supply due to disease out-breaks, natural disasters, and when manufacturers choose to stop producing or are experiencing production problems. Only 4 % of the products counterfeited were in shortage (Figure 26).

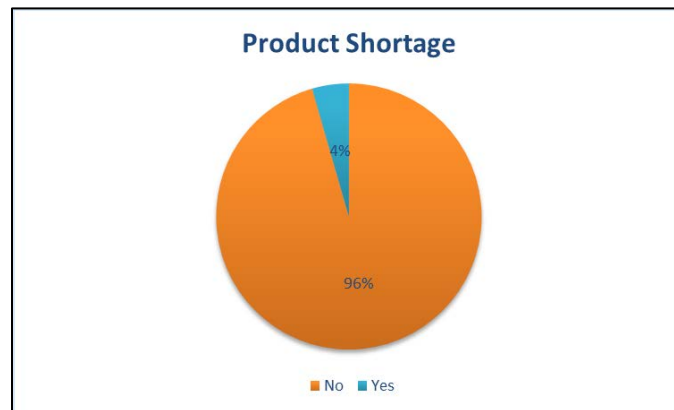


Figure 26: Product Shortage

4.4.9 Previous Product Counterfeiting

The dataset revealed approximately 43% of products counterfeited had been counterfeited in the past and approximately 57% had no previous counterfeiting history (Figure 27).

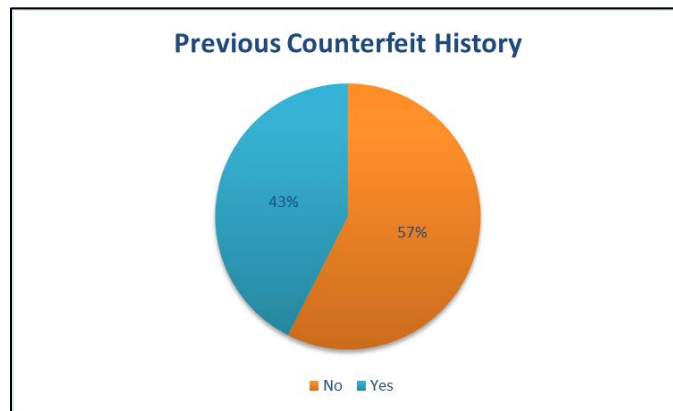


Figure 27 : Previous Counterfeit History

4.4.10 Product Location

Table 13 presents where and in some instances by which the products were discovered in the supply chain. Locations such as internet, illicit manufacturers, and pharmacies were the most prevalent supply chain location where counterfeit products were discovered. Customs, distributors, and law enforcements were methods through which counterfeit products were found.

Table 14: Discovery Method and Product Location

Discovery Method	Frequency	Percent
Broker	2	1.49%
Custom	26	19.40%
Distributor	9	6.72%
Doctors	2	1.49%
Hospital	4	2.99%
Internet	20	14.93%
Mail Facility	1	0.75%
Manufacturer (Illicit)	19	14.18%
Online Pharmacy	6	4.48%
Other	2	1.49%
Patient	1	0.75%
Pharmacy	20	14.93%
Law Enforcement	2	1.49%
Private Business	5	3.73%
Retail	1	0.75%
Supplier	2	1.49%
Warehouse	3	2.24%
Wholesaler	9	6.72%

Chapter 5: Data Analysis and Discussion

5.1 Introduction

This chapter presents an overview of factor analysis and the results of its application to ten counterfeit attributes that were subsequently reduced to three explanatory factors. Also presented are the results of analyses conducted on drug counterfeit attributes data to determine (1) the empirical relationship of counterfeit attributes to explanatory factors (2) the empirical significance of each factor, and (3) a qualitative validation of the factors against the expert survey results.

5.2 Factor Analysis

This research utilized factor analysis (FA) to analyze counterfeit variables and their importance for ranking drugs at risk of being counterfeited. This FA approach was selected to reduce the initial number of counterfeit attributes to a small number of critical factors. This small number of critical factors typically explains most variability in the original measures (Sheskin, 2007). The fundamental assumption of FA is that there are underlying influences in the data, and these influences manifest in patterns of variance that move together (Groth, 2009). Table 14 lists statistical terms with definitions that are commonly used in factor analysis.

Table 15: Factor Analysis Statistical Terms

Term	Definition
Variance	Variance indicates the degree of dispersion (or spread) of the data. In simple terms, variance is the averaged squared-difference between values of the individual data points and the mean of the data.
Factor	A linear combination of variables, any combination, constitutes a factor.
Factor Loadings	Factor Loadings are the correlations of the variables with the factor (unobserved factor).
Correlations	In factor analysis, correlation coefficients are used to express relationships between variables. For example, the closer to zero a coefficient is, the less the relationship between the variables; the closer to one, the greater the relationship. Negative represents an inverse relationship. A correlation coefficient is interpreted by squaring it and multiply by 100. This gives the percent shared variation between two variables.

Exploratory Factor Analysis (EFA) can be used to analyze the structure of a set of variables or when the latent structure of data is unknown or uncertain (Kim & Mueller, 1978). In EFA, the variance in the observed data is created by several measured variables as well as by invisible factors that influence the variables. Each variable is the linear combination of its underlying influence [I] and a number of common influences [C], plus error (see Figure 28). The sum of these underlying variables results in an observable factor (Groth, 2009).

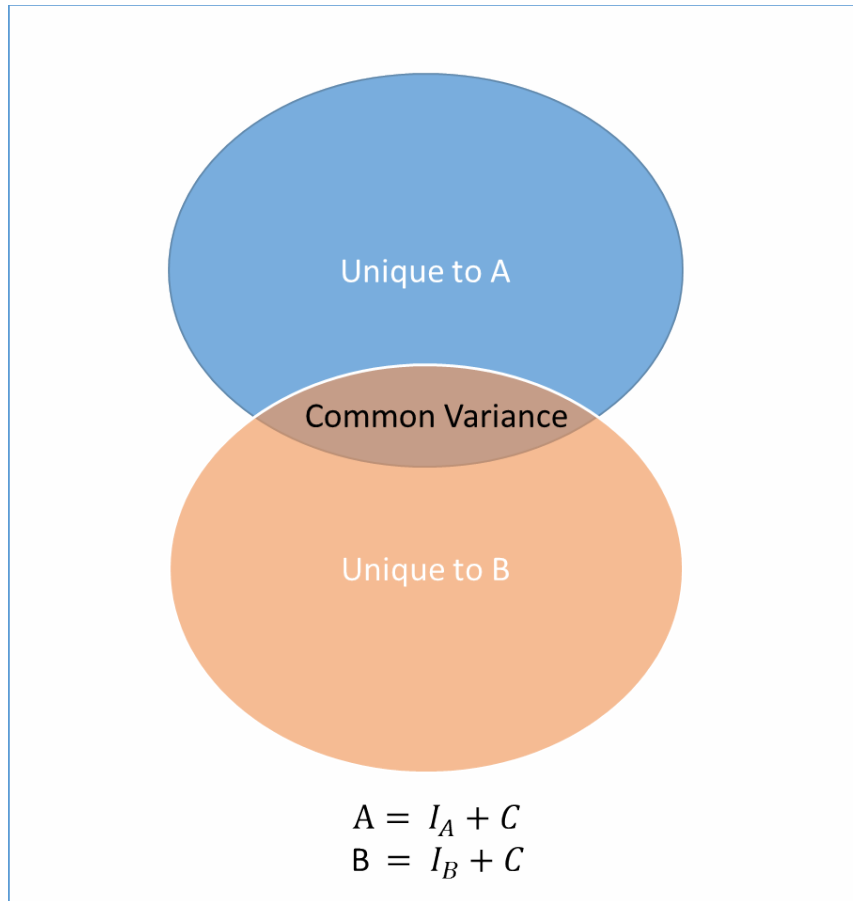


Figure 28 : EFA – Product of Underlying individual influence [I] and communality (common) influences [C]. (Groth, 2009)

EFA was used for the following reasons:

1. The multivariate data collected in this study were comprised of 10 counterfeit attributes but we have limited understanding of their relationships to one another
2. EFA is powerful in extracting a small number of hidden factors in multivariate data, which could explain most of the variation in the data; and

3. EFA can handle multicollinearity (e.g., variables that are highly correlated with each other) to produce stable and meaningful estimates for regression coefficients (Fekedulegn et al., 2002).

5.2.1 Factor Analysis Basics

A factor is an unobserved variable or a condensed statement of the relationships among a set of variables (Kline, 1994). In the example of Figure 29, the researcher assumes a structure prior to applying EFA. After EFA is applied, the researcher discovers that only two variables are relevant: Arithmetic and Geometry. After additional analysis, the research determines the unobserved factor that these variables describe is math ability. The unobserved factor was determined through the correlation between factors and variables.

This correlation is referred to as a *factor loading*. Factor loadings are used to quantify the importance of a factor in explaining the variances of the variables. It is especially important in interpreting and naming factor(s) discovered in the analysis.

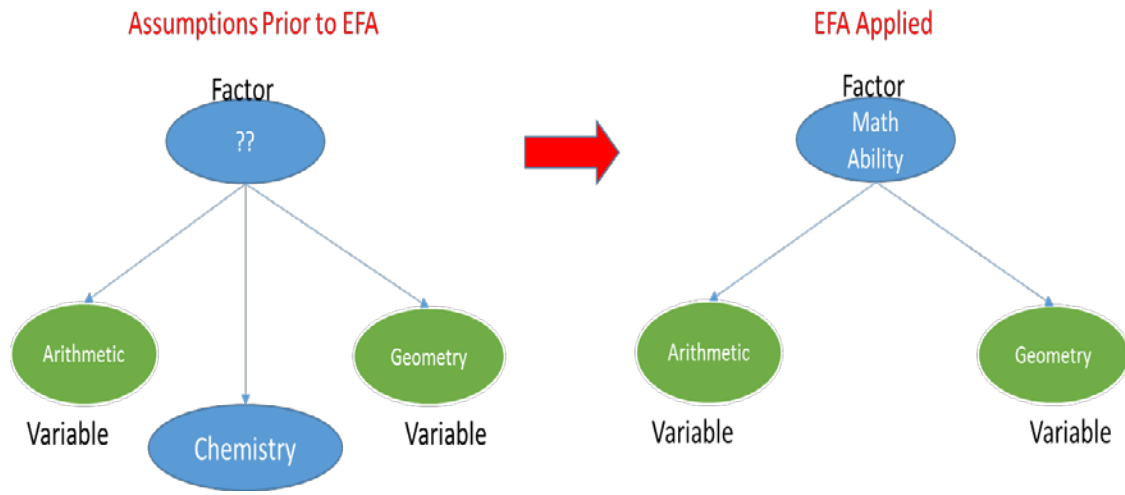


Figure 29 : Example of Factor and Variable Relationship

(Source: <https://assessingpsyche.files.wordpress.com/2014/01/independentfactors1.png>)

5.2.2 Process and Mathematics of Factor Analysis

Figure 30 shows the factor analysis process. There are three important statistics in factor analysis: the means of variables, the variances of the variables, and the correlations among variables. The mean indicates the central tendency of a variable and variance indicates the degree of dispersion.



Figure 30 : Factor Analysis Process (Kline, 1994; Kim & Mueller, 1978)

5.2.2.1 Data Screening

Data screening is the first step in factor analysis. According to Kim & Mueller (1978), it is important to examine the correlation between the variables by creating a correlation matrix of all variables. The correlation matrix in factor analysis represents the correlation coefficients that are used to express relationships between variables. For example, the closer to zero a coefficient is, the less the relationship between the variables; the closer to one, the greater the relationship. Negative represents an inverse relationship. A correlation coefficient is interpreted by squaring it and multiplying it by 100. This gives the percent shared variation between two variables.

This first step is important because it allows us to remove variable(s) that are measuring that are highly correlated. The second step in data screening is to ensure that all the variables in the study are standardized. Specifically, if the original variables are in different units, ensure all variables are standardized into one unit. For example, if a variable is expressed in ounces, its variance will be $16 \times 16 = 256$ times of that expressed in pounds. Then this variable will have more influence on the factor, and the original variables have different meanings and different numerical magnitude. For example, one variable measure in inches and another measuring pressure. Standardizing the variables ensures that the results of analysis are reliable (Young and Sarle, 1983).

5.2.2.2 Factor Extraction

Two widely used factor extraction methods are maximum likelihood and principal axis factoring. These extraction methods (or analyses) determine how well the factors explain the variance in the data. Maximum likelihood estimation is used when the data are normally distributed and principal axis factoring estimation makes no assumption about the type of error or distribution types.

The most important analysis or step in factor analysis is factor extraction. This portion of the analysis have some analyst subjectivity. Fortunately, there are several guidelines to alleviate the challenge in extracting and interpreting factors. The most commonly used techniques are the Kaiser-Guttman rule and the scree test.

The Kaiser-Gutman rule is based on three principles: (1) obtain the eigenvalues derived from the correlation matrix; (2) determine how many eigenvalues are greater than 1.0; and (3) use the number to determine that latent dimensions. The fundamental idea behind the Kaiser-Guttman rules is that when the eigenvalue is less than 1.0, the variables explained by the factor is less than the variance of a single indicator. The eigenvalue measures the variance in all the variables, which is accounted for by that factor. Therefore, if a factor has a small eigenvalue, then it is contributing little to the explanation of the variances in the variables and may be ignored (Brown, 2009).

The *Scree test* uses the eigenvalue to reduce the number of factors in the solution. It is a visual depiction of the eigenvalues to determine their importance (see Figure 31). The principle behind the scree test is that the important factors will have the higher eigenvalues which indicate that they also have larger variance.

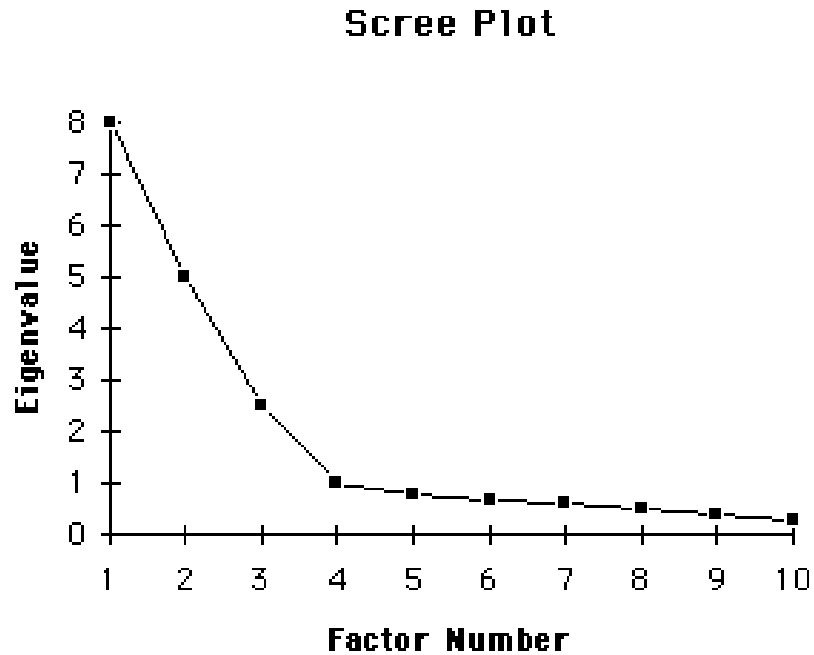


Figure 31 : Scree Test Plot

5.2.2.3 Factor Rotation

In factor analysis, the various extraction methods seek to extract a set of factors from the data. Initially, these factors are orthogonal to one another and ordered according to the proportion of the variance that the factor explains. However, this first extraction does not explain or make the results understandable, therefore, rotation makes the results more understandable by seeking the most meaningful and simple structure (see Figure 32) (Hair et al., 1998).

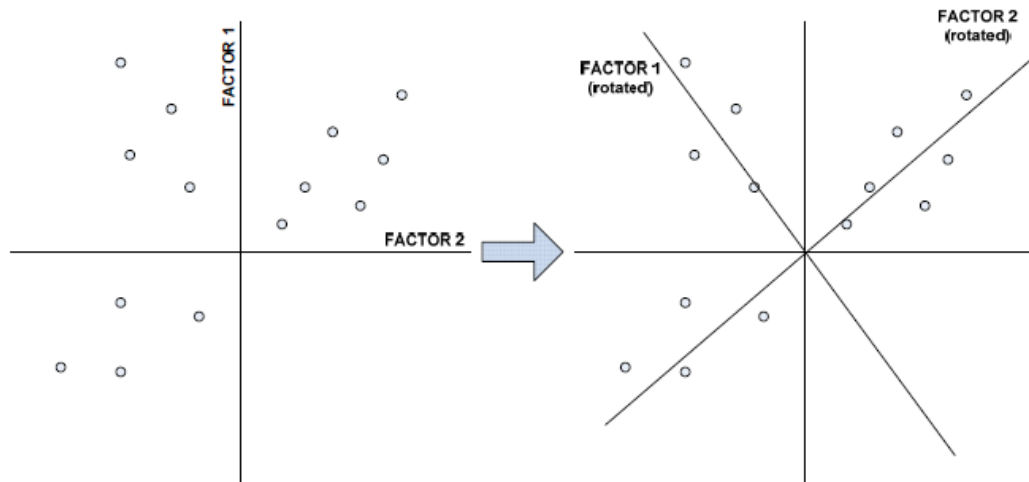


Figure 32 : Concept of Factor Rotation

In general, there are two types of factor rotation used: orthogonal and oblique. Orthogonal rotation or solutions seek to find factors that are uncorrelated (Hatcher, 1994). According to Kieffer (1998), orthogonal rotation “shifts the factors in the factor space maintaining 90 degrees angles of the factors to one another to achieve the best simple structure.” This facilitates the uncorrelated nature of the factors after the factors are rotated and provides easier interpretation of the analysis. Two types of orthogonal rotation methods used in factor analysis are varimax and quartimax rotation.

Varimax rotation is the most used orthogonal rotation methods developed by Kaiser. Varimax method enables clearer depiction of large factor pattern/structure coefficient on only one of the factors. This method produces factors that have larger structure coefficients for a small number of variables and near-zero coefficients with the other group of variables (Kieffer, 1998). Quartimax rotation method forced the variable to

correlate highly with one main factor and very little with the remaining factors (Kim & Mueller, 1978). This enables easier interpretation of the variable because one the variables load toward a single factor.

Orthogonal rotation provides us with several advantages (Kieffer, 1998):

1. Factors remain perfectly uncorrelated with one another and are inherently easier to interpret; and
2. Factor pattern matrix and structure matrix are equivalent; ensures solutions that are more meaningful.

Oblique rotation provides correlations among the latent construct (Kim, 1978). The method is oblique because the angles between the factors become greater or less than the 90-degree angle. Promax and direct oblimin are two popular oblique rotation methods. The promax technique attempts to achieve the most parsimonious structure by allowing the factors to correlation with one another. There are three steps in the promax rotation (Kieffer, 1998):

1. Rotate factors orthogonally;
2. Raise the factor pattern coefficients to an exponent greater than two; and
3. Rotation of the original matrix to a best-fit position with the target matrix.

The direct oblimin rotation method is driven by the “delta-value” concept that is typically chosen by the researcher. In this approach, positive values would generate larger correlations coefficients between factors and negative values would generate smaller correlations coefficients between factors. The strength of the direct oblimin method is

that it allows researchers to map out the research objectives and relationship amongst the variables, as the correlations must be decided prior to the analysis (Kieffer, 1998).

5.2.2.4 Factor Interpretation

The last part of the factor analysis is to explain the factor results. In factor analysis, the factor that explained the least variance is removed from the analysis. In the wealth example provided in Table 15, only two factors are retained – Factor 1 and Factor 2. The numbers (factor loadings) depicted in the table express the relationship between the factor and the variable. The variable with the strongest relationship to factor is retained to that specific factor as it explains the factor the most. For example, Factor 1 is income, as it has the highest factor loading of 0.65. Since factor loadings can be interpreted as standardized regression coefficients, the relationship between the factor and the variable can be viewed as correlation as well (Rahn, 2015).

Table 16 : Factor Interpretation (Rahn, 2015)

Variables	Factor 1	Factor 2
Income	0.65	0.11
Education	0.59	0.25
Occupation	0.48	0.19
House value	0.38	0.6
Number of public parks in neighborhood	0.13	0.57
Number of violent crimes per year in neighborhood	0.23	0.55

The second part of the factor analysis is assessing the statistical significance of factor loadings. To assess the statistical significance of the factors it is important to understand the practical and statistical significance (Hair et al., 1998).

Practical Significance: According to Hair et al. (1998) the approximations provided in Table 16 is more a rule of thumb used frequently to make a preliminary examination of the factors. In short, factor loadings (*i.e.*, correlations of the factors with the variables) greater than ± 0.30 are considered to be minimally important; loadings of ± 0.40 are considered important, and loadings of ± 0.50 are considered practically significant, Thus the larger the absolute size of the factor loading, the more important the loading in interpreting the factor. Because the factor loading is the correlation of the variable and the factor, the squared loading is the amount of the variable's total variance account for the factor.

Table 17 : Factor Significance Based on Sample Size (Hair et al., 1998)

Factor Loading	Sample Size
0.40	200
0.45	150
0.50	120
0.55	100
0.60	85
0.65	70
0.70	60
0.75	50

5.3 Drug Counterfeit Factor Analysis

The data collected for this research is discussed in Chapter 4; it consists of 10 counterfeit attributes for analysis. First, a principle axis factoring method is applied to extract the initial factors and the varimax method is applied to rotate the factors to gain an interpretation of the factors. SAS® statistical software package was used to conduct the factor analysis. The result is presented in Table 17.

Table 18: Initial Factors Extraction

Attributes	Factor 1	Factor 2	Factor 3
Medication Class (mc)	0.9010	0.1258	0.1051
Volume (vlm)	0.6033	-0.1518	-0.4554
Average Price (avp)	0.9452	0.0012	0.1637
Product Location (pl)	0.0327	0.7900	-0.0313
Product Type (pt)	0.8776	0.1355	0.1431
Product Complexity (pc)	-0.0516	0.8641	-0.2882
Product Shortage (ps)	-0.1488	0.0255	0.8480
Previous Product Counterfeit (ppc)	-0.2965	0.0526	0.4435
Region (rg)	0.0022	0.6390	0.1294
Drug Class (dc)	0.6811	0.4762	-0.5967

The number of factors to retain was based on the eigenvalue scree test (see Figure 33). The scree test uses the eigenvalue to reduce the number of factors in the solution. It is a visual depiction of the eigenvalues to determine their importance. Eigenvalues greater than one were retained as they explained the greatest amount of variance in the data set.

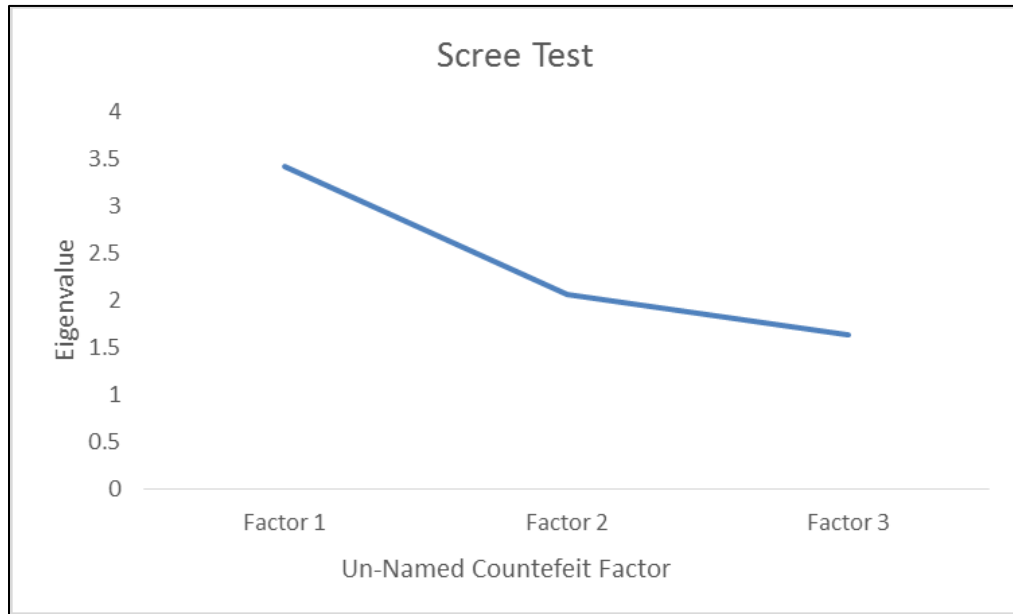


Figure 33: Scree Test for Eigenvalues

In interpreting the factors in this study, a variable was said to load on a given factor if the factor loading was greater than .45 based on the sample size of 134. Using these criteria, five variables were found to load on the first factor (*i.e.*, the first factor had correlations of absolute value greater than 0.45 with five of the variables); three variables were found to load on the second factor, and two variables we found to load on the third factor (Table 18).

Table 19 : Assessing Factor Significance

Attributes	Factor 1	Factor 2	Factor 3
Medication Class (mc)	0.9010	0.1258	0.1051
Volume (vlm)	0.6033	-0.1518	-0.4554
Average Price (avp)	0.9452	0.0012	0.1637
Product Location (pl)	0.0327	0.7900	-0.0313
Product Type (pt)	0.8776	0.1355	0.1431
Product Complexity (pc)	-0.0516	0.8641	-0.2882
Product Shortage (ps)	-0.1488	0.0255	0.8480
Previous Product Counterfeit (ppc)	-0.2965	0.0526	0.4435
Region (rg)	0.0022	0.6390	0.1294
Drug Class (dc)	0.6811	0.4762	-0.5967

Table 20: Final Counterfeit Factors with Attributes and Loadings

Factor	Attribute	Factor Loading (correlation)
Factor 1	Average Price	0.945
	Drug Class	0.681
	Medication Class	0.901
	Product Type	0.878
	Volume	0.603
Factor 2	Product Complexity	0.864
	Product Location	0.790
	Region	0.639
Factor 3	Previous Product Counterfeiting	0.443
	Product Shortage	0.848

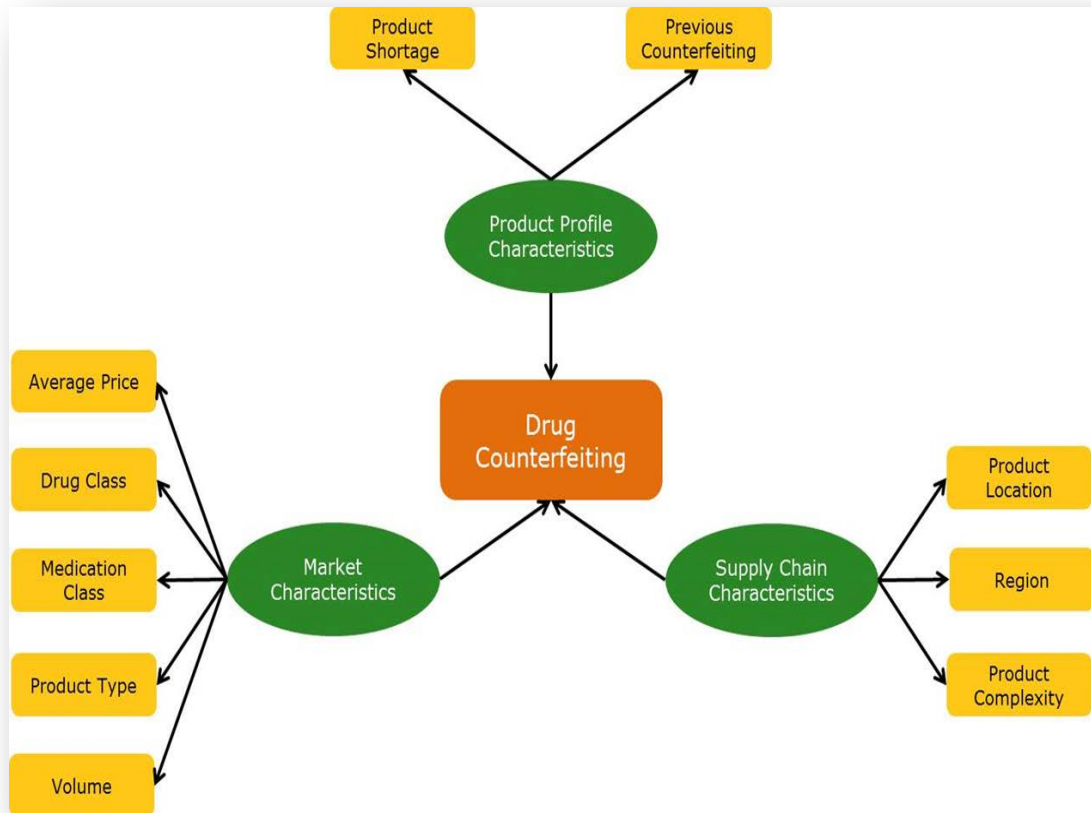


Figure 34 : Conceptual Model for Drug Counterfeiting

5.3.1 Factors Label

The exploratory factor analysis of ten counterfeit attributes for Tables 19 and 20 yielded three dimensions of factors. These dimensions were described as Market Characteristics (MC), Supply Chain Characteristics (SCC), and Product Profile Characteristics (PPC) (see Figure 34). “Market Characteristics” consist of average price, drug class, medication class, product type, and volume. “Supply Chain Characteristics” consist of product complexity, product location, and region. “Product Profile Characteristics” consist of previous product counterfeiting and product shortage.

5.3.2 Enhanced Factors Significant Testing via Regression Analysis

Following the identification of the new counterfeit factors, regression analysis was used to test their statistical significance. Statistical significance is when the *p-value* is less than significance level. That is, “*the p-value is the probability of observing an effect given that the null hypothesis is true whereas the significance or alpha (α) level is the probability of rejecting the null hypothesis given that it is true*” (Schlotzhauer, 2007). Each factor’s significance was tested against the outcome or response variable, which was chosen as the percentage of drug product counterfeited (CFT) in the past.

The percentage of counterfeited drug used to determine factor significance, was obtained from publically available data (e.g., WHO, published journals, and PSI). It was not feasible to account for all counterfeit medicines by product type. To account for missing medication class data, a default 10% was used based on WHO estimates that approximately 10% of drugs worldwide are counterfeited (WHO, 2006).

Standard multiple regression was used to test the relationship between factors (independent variable) and CFT (dependent variable). Multiple regression analysis was used to derive a linear equation that would best fit the relationship between the independent variables and dependent variable (Ross, 1987).

To determine factor significance identified in this study, a sum score method was used. In factory analysis, sum scores are used to develop factor scores so that regression analysis can be applied (DiStefano et al., 2009). Sum score by factor involves summing raw scores corresponding to all variables loading on a factor (DiStefano et al., 2009). For example, if a factor has a negative loading, the raw score of variable is subtracted rather than added in the analysis because the variable is negatively related to the factor. The sum score method is most desirable when the scales used to collect the original data are “untested and exploratory” (Hair et al, 2006). In addition, the sum score method preserves the variation in the original data.

A regression analysis was performed on CFT against the independent variables MC, SCC, and PPC (Table 21). The estimates are statistically significant at the $p < 0.05$ level for MC and SCC but not for PPC.

Table 21: Regression Results

Predictor	Coef	SE Coef	T	P	
Constant	-35.165	7.432	-4.73	0	
MC	14.576	2.002	7.28	0	
SCC	25.4	11.78	2.16	0.033	
PPC	29.53	26.41	1.12	0.266	
<i>S</i>	<i>11.5034</i>	<i>R-Sq</i>	<i>31.60%</i>	<i>R-Sq(adj)</i>	<i>0.300</i>

Where:

Coefficients (**Coef**): Parameters of the Model

Standard Error of Coefficients (**SE Coef**): Standard Error of the estimators

T - Test: The t-test is used to test the significance of the model parameters and the response variable. The null hypothesis $H_0: \beta_1 = 0$: no significant relationship between the significant variable and independent variable(s) against $H_a: \beta_1 \neq 0$: significant relationship exists.

The results presented in Table 21 indicated the MC and SCC are statistical significant on $\alpha = 0.05$ when there regressed on counterfeit percentage data. Furthermore, PPC was not a significant factor, however, it was factor retained for model development based on experts and case studies evaluation.

5.4 Qualitative Validation

The model presented in Chapter 3 is important for three primary reasons: (1) to provide new variables for this study; (2) to validate existing and new variables previously identified through analysis of literature and an expert elicitation process; and (3) to provide qualitative validation that this model could be used in a decision-making context. The expert selection process, as well as the qualitative validation of counterfeited attributes, and a discussion of their influence on prioritizing products at risk of counterfeiting was previously discussed in Chapter 3.

Experts provide their opinion about the degree of influence each variable has on counterfeiting. These experts indicate their opinion about the degree of influence as:

Very Strong Indicator (+++)

Strong Indicator (++)

Good Indicator (+)

Although the attributes were quantitatively validated and the factors validated through multivariate techniques, it is worth combining both analysis to see the differences (see Tables 22 & 23). If more than three experts responded with a very strong indication; the consensus is that the variable is a very strong indicator; if more than three responded with a combination of very strong and strong indicators, the consensus is a strong indicator; if more than three experts responded with a good indicator; the consensus is a good indicator.

Table 22: Experts Survey Responses

Variables	Expert 1	Expert 2	Expert 3	Expert 4	Expert 5	Expert 6
Average Price	+++	++	+++	+++	+++	+++
Drug Class	++	++	+++	+++	++	+++
Medication Class	++	++	++	+++	+++	++
Previous Product Counterfeiting	+	+	++	+	++	+
Product Complexity	++	++	++	++	+	++
Product Location	++	+	+++	++	+	+++
Product Shortage	+	+	++	NR	+	++
Product Type	++	+	++	++	+	++
Region	+++	++	+++	++	++	+++
Volume	++	+	+++	++	+	++
<p>+++ = Very Strong Indicator ++ = Strong Indicator + = Good Indicator NR = No Response</p>						

Table 23 : Qualitative Validation of Results

Factors	Variables	Expert Consensus	Factor Analysis Result
MC	a. Average Price	a. Very Strong	a. 0.945
	b. Drug Class	b. Strong Indicator	b. 0.681
	c. Medication Class	c. Strong Indicator	c. 0.901
	d. Product Type	d. Strong Indicator	d. 0.878
	e. Volume	e. Strong Indicator	e. 0.603
SCC	a. Product Complexity	a. Strong Indicator	a. 0.864
	b. Product Location	b. Strong Indicator	b. 0.790
	c. Region	c. Very Strong	c. 0.639
PPC	a. Previous Product Counterfeiting	a. Good Indicator	a. 0.443
	b. Product Shortage	b. Good Indicator	b. 0.848

5.5 Discussion and Implications

5.5.1 Market Characteristics

The results in Tables 20, 21, 22, and 23 represent salient findings that contribute to understanding the counterfeiting of pharmaceutical drugs. First, the results show that average price and medication class heavily influence the market characteristics factor. While other researchers published that price and medication class attributes are good indicators of a product's risk of being counterfeited, they fail to identify the empirical relationship of these attributes to a common Factor. We further identified through multivariate analysis and expert opinion that these are "very strong" and "strong" indicators for ranking drugs at risk of counterfeiting. Regression analysis of the factor data indicated that is a statistically significant factor for determining drugs at risk of counterfeiting. Both factor analysis and experts indicate a consensus that the market characteristics factor is a strong predictor. Several variables such as drug class, product

type, and volume are loaded on MC in the order: Average Price, Medication Class, Product Type, Drug Class, and Volume.

The results of this finding are in-line with other research (Spink, 2009; OECD, 2007; Staake et. al, 2010). Market characteristics can also be viewed as the counterfeiter's willingness (ability) to produce a fake drug product. It is well known that counterfeiters often target products (e.g., drugs) that they can easily deceive authorities by their physical appearances.

Bates (2008) further classified this finding, in that, counterfeiters target medication class based on the country the products are intended to be marketed. For example, counterfeiters target the counterfeiting of life style drugs in developed countries and anti-malarial drug products in less developed countries. He stated that counterfeiters are beginning to target lifesaving drugs through traditional supply chains, which pose a great public health risk. Taking the drug medication class and volume into the drug prioritization framework, enables decision makers to focus on current and future threats in the drug supply chain.

Average price and drug class can be viewed as another "Baiting-Element" for counterfeiters. Drug class in this study is defined as either prescription (Rx) or over-the-counter (OTC) products. Typically, prescription products usually have a higher profit margin. It is not surprising to see these two attributes are loading on MC as it is key

indicator for counterfeiters to get into the market. The baiting feature is the ability for the counterfeiter to make profit considering other costs such as production and cost to put fake products into the supply chain (Kontik, 2004; OECD, 2007b; Spink, 2009). The average price is a true indication as to why pharmaceutical counterfeiters enter the market. According to Staake et al. (2010), these features attract “*Desperados*.” Counterfeiters usually target expensive products, easy to mimic, and whose quality is difficult to evaluate prior to purchase (Staake et al., 2010). It is important to mention that in this study, we discovered that the majority of the counterfeited brand-name products were prescriptions products. Pharmaceutical counterfeiting, however, is a still valid result and is in-line with other studies completed by Staake (2010) and Spink (2009).

The volume attribute can be viewed as a “demand” factor. The result indicates that volume influences counterfeiters and the pharmaceutical products they target. In a decision making context, the amount of products available, by itself, is not a clear indicator that it will be counterfeited. Including volume will enable decision makers to see the landscape of potential products at risk of being counterfeited.

5.5.2 Supply Chain Characteristics

Supply chain characteristics factor (SCC) is measured by product complexity, product location, and region. From the analysis, we discovered that product complexity and product location heavily influence the supply chain characteristics. From the regression analysis, the SCC factor is significant in the model and is a useful for ranking drugs at risk of counterfeiting. We also discovered through factor analysis, that the variables are all significant based on the factor-loading test. Experts also validated that these variable are strong indicators for determining drug at risk of counterfeiting.

According to Staake et al. (2010), product complexity is defined as the visual, functional, and intricacy of a drug. Experts identified “product complexity” as one of the most important characteristics of counterfeited articles. For example, brand names products are often counterfeited more than generic products because of their high profit margins. However, if the profit margin is the same between generic and brand name products, counterfeiters are indifferent as to which type of drug to produce. What makes a difference are logo-counterfeiting and the availability to production machinery (Stake et al., 2010). Logo-counterfeiting is expensive especially for some brand name products.. However, the increasing availability of production components makes it easier for counterfeiters to produce fake products.

Product location variable is also a significant component of the supply chain characteristic (SCC) factor. The location or region, in which drug ingredients are

purchased, final products are manufactured or sold, plays an important role in drug counterfeiting and potential harm to consumers. This is also a critical element to include in the drug prioritization model. Because, it allow decision makers to allocate resources in critical areas to sample and test drug products. In a study conducted by Opsec (2009), they found that internet pharmacies 50 % of cases when drug are purchased from internet sites conceal their actual physical address as well as provide false location of operation. They also found that many consumers are not aware that low price drug maybe an indicator that a drug contains substandard active ingredient or may come from an unregulated regions. With the pharmaceutical landscape rapidly changing; the manufacturing of drug products occurring at a global level and with the advent of technology (e.g., internet), counterfeiters are utilizing the full bandwidth to introduce counterfeit products into the legitimate supply chain.

5.5.3 Product Profile Characteristics

The third counterfeit factor, product profile characteristics (PPC) comprises product shortage and previous counterfeiting attributes. Both attributes are found in more recent incidences of counterfeited drug products, and are becoming more attractive to counterfeiters. Through regression analysis, this factor was not significant. However, through factor analysis the variable themselves were significant and were kept in this research. Experts also validated these variables as good indicators for determining drugs at risk of counterfeiting. Furthermore, it was evident from drug counterfeiting data used in this research, that product shortage and drugs with previous counterfeiting history are both good indicators for potential drug counterfeiting.

Cherici et al. (2011) provides some insights into the connection between drug shortages and the potential for counterfeiting. They discussed when products are scarce or in short supply, gray markets (parallel markets) inevitably becomes a source that introduces counterfeit products into the legitimate supply chain. Cherici et al. stated,

In times of shortage, pharmacies may have no choice but to purchase from companies that are not among traditional contracted supplies. Most of the time, these suppliers are legitimate companies. But hiding in their midst are gray market impersonators.

It is coincidental that product-shortage and previous counterfeiting variables load on the same factor. Previous counterfeiting is an important lagging attribute, in that; it educates decision makers about the products that were previous counterfeited and strategies that were taken to help to survey and test products. At the same time, this factor will ensure that similar medication class types counterfeited in the past are taken into consideration during the decision making for analysis.

5.6 Implications for Private and Regulator Decision Makers

As noted in the previous chapters, this research provides supply chain risk managers and other decision makers with a framework for understanding the factors that influence drug counterfeiting and provide empirical evidence about the factors differences on counterfeiting. The conceptual framework along with the empirical evidence is useful on two levels, an industry level and drug regulatory level. At the industry level, the framework helps supply chain managers to understand the interrelations among the variables and their overall contribution to the decision making for various initiatives. These initiatives include procuring products, supply chain validations, security polices, and advancing anti-counterfeiting technologies to protect branded and generic products. At the regulatory level (government), the framework can be used to prioritize drugs at risk of counterfeiting in a given inventory and to develop new policies to better target drugs in the supply chain at risk of counterfeiting.

From a market characteristics perspective, this analysis suggests that both regulatory and private entities focus on medication class and average unit prices. Other researchers (Spink 2009, OECD, 2007) suggested using all attributes in a decision model without prioritizing their importance. This study suggest if resources (e.g., monetary) are limited, it is reasonable to focus on average unit price, medication class, and product type (e.g., brand or genic product).These attributes are good indicators to predict drug counterfeiting.

Furthermore, this research also highlighted another very critical factor, the supply chain characteristics. This analysis suggests that regulatory and private entities should focus on country of origin and product location (or supply chain location) as good indicators to predict drug counterfeiting.

Chapter 6: Model Development for Assessing the Likelihood of Drug Counterfeiting

6.1 Introduction

This chapter presents the development of the drug counterfeit model and its subsequent validation. The model expresses an empirical relationship between the counterfeiting risk attributes of a pharmaceutical drug product and the likelihood of product being counterfeited. The resulting relationship enables ranking drug products by the likelihood of counterfeiting.

Using the set of risk attributes discussed in previous chapters, a dataset was built from known counterfeit cases. The dataset includes the following attributes:

- Average Price
- Drug Class
- Medication Class
- Product Type
- Volume
- Product Complexity
- Product Location
- Region
- Previous Product Counterfeiting
- Product Shortage

The ten risk attributes were grouped to three factors: Product Profile Characteristics (PPC), Market Characteristics (MC), and Supply Chain Characteristics (SCC).

This chapter explains the drug counterfeit model development and validation steps (Figures 35).

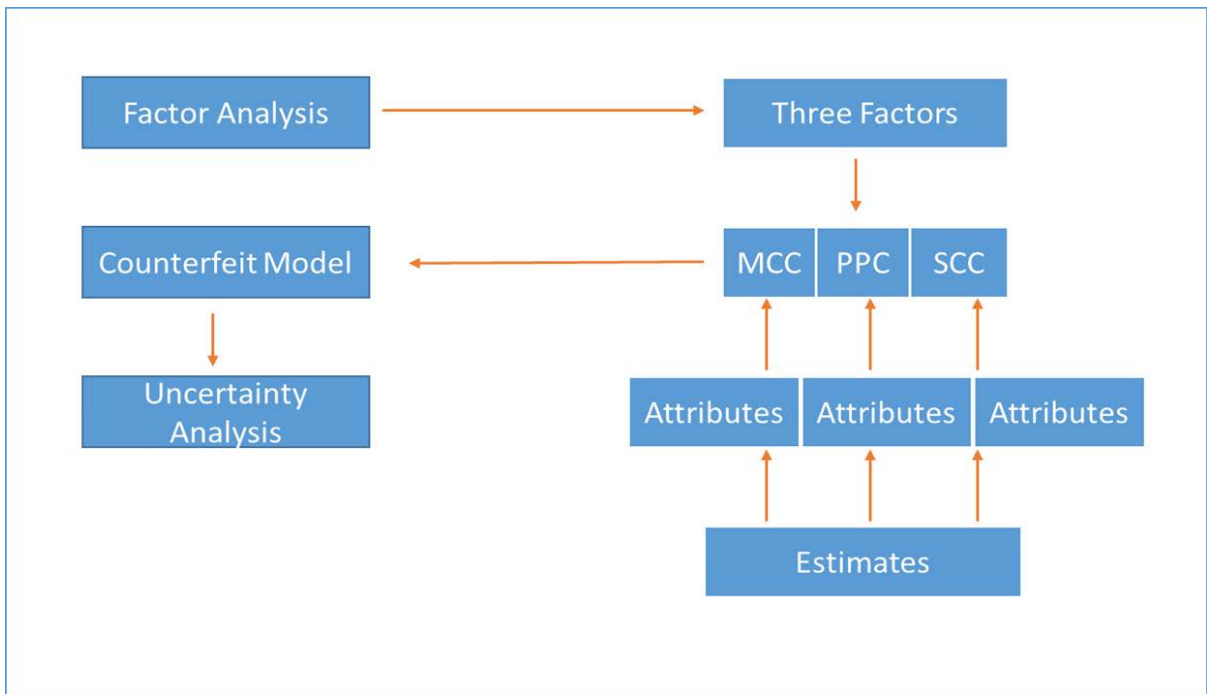


Figure 35: Modeling Framework

Figures 35 depict the process to determine the likelihood of drug counterfeit. The models presented in the previous sections were combined to generate drug composite counterfeit scores (CCS). These CCS were derived from the addition of the three factors: MCC, PPC, and SCC. The CCS by themselves does not indicate the likelihood of drug counterfeit but rather a drug composite score. The subsequent sections outline the

proposed approach for obtaining a drug composite score and determining the likelihood of drug counterfeit

6.2 Drug Counterfeit Model

We propose a linear model for predicting drug products at risk of counterfeiting:

$$\text{Composite CFT Score} = \beta_0 + \beta_1 \text{MC} + \beta_2 \text{SCC} + \beta_3 \text{PPC} \quad \text{Equation 6-1}$$

Where:

Composite CFT Score: drug counterfeit propensity score

MC: Market Characteristics

SCC: Supply Chain Characteristics

PPC: Product Profile Characteristics

Market characteristics (MC) are average price, drug class, medication class, product type, and volume. Market characteristics are modeled as:

$$\text{MC} = x_p + x_c + x_t + x_{mc} + x_v \quad \text{Equation 6.2}$$

Where:

Attribute Name	Attribute Characteristic	Attribute Index
<i>Drug Price</i>	x_p	p = Average Unit Drug Price
<i>Drug Class</i>	x_c	c = [OTC or Rx] 0 = OTC 1 = Rx
<i>Product Types</i>	x_t	t = [Generic or Brand] 0 = Generic 1 = Brand
<i>Medication Class</i>	x_{mc}	mc = 1...20 [see Table 24]
<i>Drug Volume</i>	x_v	v = volume for each drug

Supply chain characteristics (SCC) are modeled as:

$$SCC = x_l + \sum_{r=0}^5 x_r + x_{pc} \quad \text{Equation 6.3}$$

Where:

Attribute	Attribute Characteristics	Attribute Index
<i>Product Location</i>	x_l	l = [location] 0 = low risk location 1 = high risk location
<i>Region</i>	x_r	r = [geographic location] 0 = Africa, 1 = Asia, 2 = Europe, 3 = Latin/South America, 4 = Middle East, 5 = North America
<i>Product Complexity</i>	x_{pc}	pc = [complexity] 0 = noncomplex 1 = complex

Product profile characteristics are model as:

$$PPC = x_s + x_h \quad \text{Equation 6.4}$$

Where:

Attribute Name	Attribute Characteristics	Attribute Index
<i>Product Shortage</i>	x_s	s = [shortage] 0 = Drug not in shortage 1 = Drug in shortage
<i>History of Counterfeit</i>	x_h	h = [counterfeit history] 0 = no previous counterfeit 1 = previously counterfeited

The model presented in Equation 6.1 is the first step toward quantifying the probability of products at risk of drug counterfeiting. Figure 35 depicts the process of the obtaining likelihood of drug counterfeit.

6.3 Estimating Attribute States

An empirical probability (relative frequency) approach is used to estimate the attribute states from the data collected. The empirical probability (relative frequency) is obtained by dividing the frequency for that class by the total number of observations (Jaisingh, 2000).

The empirical probability is estimated through the following:

$$f_i = \frac{n_i}{N} = \frac{n_i}{\sum_j n_j}$$

Or

$$\text{Relative Frequency} = \frac{\text{frequency of class}}{\text{total number of observations}} \quad \text{Equation 6.5}$$

6.3.1 Medication Class

The empirical probability formalism is used to approximate the values for each medication class. $P(MC_m | C)$ represents the conditional probability of a certain drug being in a medication given that it is counterfeited. From the counterfeited data gathered in this study, one can take each counterfeit case and determine its medication class. The estimated conditional probability of a drug being counterfeited (*e.g.*, $P(MC_m | C)$) is then a frequency in the data set collected.

$$P(MC_m | C) = \frac{\text{Number of counterfeit cases for specific medication class}(m)}{\text{Total Number of Counterfeited Cases}} \quad \text{Equation 6.6}$$

Table 24: Probabilities for Medication Class

Medication Class	Medication State	Probability
ACE Inhibitor	1	3.73E-02
Analgesic	2	6.72E-02
Anticoagulant	3	7.46E-03
Antidiabetics	4	1.49E-02
Anti-Infection	5	1.79E-01
Anti-Obesity	6	2.99E-02
Antipsychotic	7	2.24E-02
Anti-Viral	8	2.99E-02
Benzodiazepine	9	2.24E-02
Beta Blocker	10	2.99E-02
Birth-Control	11	7.46E-03
Life Style	12	1.94E-01
NSAID	13	2.99E-02
Oncology	14	5.97E-02
Proton Pump Inhibitor	15	7.46E-03
Statin	16	9.70E-02
Steroids	17	5.22E-02
Hormones	18	2.99E-02
Suppressants	19	5.97E-02
Vitamins	20	2.24E-02

6.3.2 Region

The attribute “region” represents the country of origin for drugs being imported into the US. As explained in chapter 4, the origin of drugs is classified into six regions: Africa, Asia, Europe, Latin/South America, Middle East, and North America. This information is dynamic and changes frequently. Information on region (i.e., country of origin) provides

intelligence on how the likelihood of drug being counterfeited is influence based on its origin. This data is utilized to form the degree of influence of region on the likelihood of drug counterfeit. Using Equation 6.7, we have the following:

$$P(RG_z | C) = \frac{\text{Number of counterfeit cases by Region}(z)}{\text{Total Number of Counterfeited Cases}} \text{ Equation 6.7}$$

$P(RG_z | C)$ represents the conditional probability of getting a certain drug from a region given that it's counterfeited. From the counterfeited data gathered in this study, one can take each counterfeit case by region, and estimate the conditional probability by its frequency. The estimates are presented in Table 25.

Table 25: Probabilities for Region

Region	Probability
Africa	8.96E-02
Asia	5.45E-01
Europe	2.31E-01
Latin/South America	3.73E-02
Middle East	7.46E-03
North America	5.22E-02

6.3.3 Drug Shortage

Drug shortage attribute represents drugs that are in shortage. Information on product shortages can be obtained through the Food and Drug Administration (FDA) and American Society of Health-System Pharmacist (ASHP). Using Equation 6.8, we

derived the following formalism to determine the degree of influence shortage history on the likelihood of a drug being counterfeited:

$$P(PS_q | C) = \frac{\text{Number of counterfeit drugs in shortage}(q)}{\text{Total Number of counterfeited drugs}} \text{Equation 6.8}$$

$P(PS_q | C)$ represents the conditional probability of a certain drug being in shortage given that it's counterfeited. From the counterfeited data gathered in this study, one can get this probability by identifying the number of drugs in shortage, and the estimated conditional probability is then its frequency. This conditional probability is presented in Table 26.

Table 26: Probabilities for Drug Shortages

Drug Shortage	Probability
Yes	4.48E-02
No	0

6.3.4 Drug Class

The attribute “Drug Class” makes a distinction between drugs that are prescription (Rx) and over-the-counter (OTC). Using Equation 6.9, we derived the following formalism to determine the degree of influence of drug class on the likelihood of a drug being counterfeited:

$$P(DC_l | C) = \frac{\text{Number of counterfeit drugs by Drug Class}(l)}{\text{Total Number of counterfeited drugs}} \text{Equation 6.9}$$

$P(DC_i | C)$ represents the conditional probability of a drug being in certain drug class (i.e., OTC or Rx) given that it's counterfeited. From the counterfeited data gathered in this study, one can get these probabilities by identifying the number of drugs in a drug class, and the estimated conditional probability is its frequency. These conditional probabilities are presented in Table 27.

Table 27 : Probabilities for Drug Class

Drug Class	Probability
OTC	1.04E-01
Rx	8.96E-01

6.3.5 Product Type

The attribute “product type” distinguishes between brand and generic products. Using Equation 6.10, we derived the following formalism to determine the degree of influence of product type on the likelihood of a drug being counterfeited:

$$P(PT_i | C) = \frac{\text{Number of counterfeit drugs by Product Type}(i)}{\text{Total Number of counterfeited drugs}} \text{ Equation 6.10}$$

$P(PT_i | C)$ represents the conditional probability of a drug being in certain product type (i.e., brand or generic) given that it is counterfeited. From the counterfeited data gathered in this study, one can get these probabilities by identifying the number of drugs in a

product type, and the estimated conditional probability is its frequency .These conditional probabilities are presented in Table 28.

Table 28 : Probabilities for Product Type

Product Type	Probability
Brand	5.45E-01
Generic	4.55E-01

6.3.6 Previous Drug Counterfeit History

To estimate the influence of previous drug counterfeit history on the likelihood of drug counterfeit, we calculated the relative frequency of medication classes that has repeated history counterfeit (i.e., more than one known cases of counterfeiting). The data collected in this study indicated that sixteen out of twenty-one medication classes had been counterfeited more than once and only five-medication class had one known history of counterfeiting. Therefore, to determine x_h , we assumed that when there is a known previous history of counterfeiting, x_h is the following (Table 29):

$$x_h (\text{yes}) = \frac{\text{Number of Medication Class Counterfeited More than Once}}{\text{Total Number of Medication Class}} \text{Equation 6.11}$$

$$x_h(\text{No}) = 1 - x_h (\text{yes})$$

Table 29 : Probabilities for Previous Drug Counterfeit History

x_h	Probability
Yes	0.71
No	0.29

6.3.7 Average Price and Volume

Both average price and volume attributes will be distribution based. Two distributions are depicted in Figures 36 & 37. The cumulative distribution functions (CDF) were derived in Minitab©. The best-fitted distribution for both variables is lognormal. Based on the distribution statistics, two CDF's were developed to best represent average price and volume attributes. Unlike the other attributes, average price and volume are a lot more complex to get estimated weights because of the different price ranges and volumes that are available within the medication class alone. It will be difficult to quantify every product with price ranges and volume. Therefore, to enable quantification of the attributes, it is convenient to extrapolate the weights from a CDF.

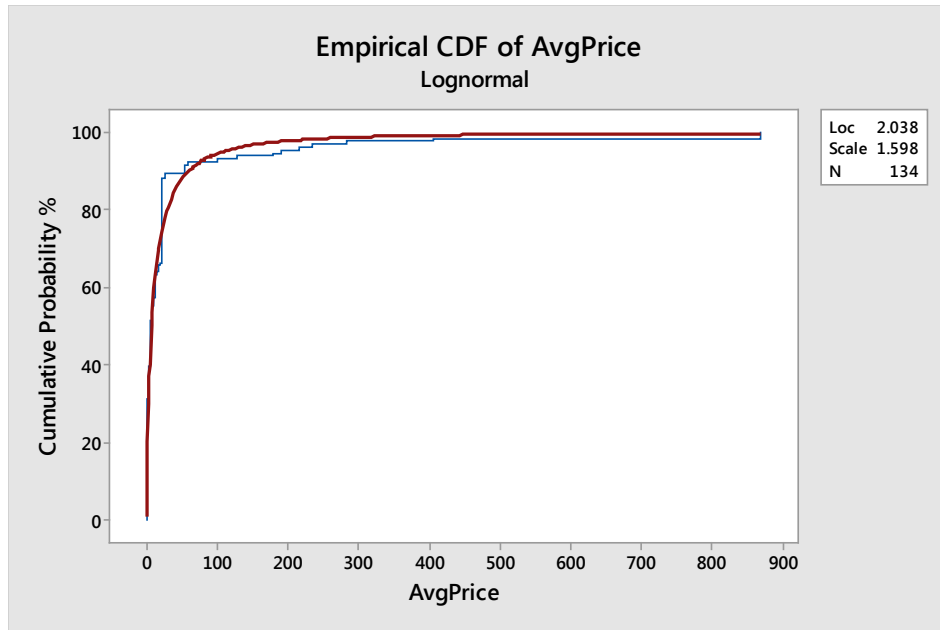


Figure 36: Cumulative Distribution Function for Average Price

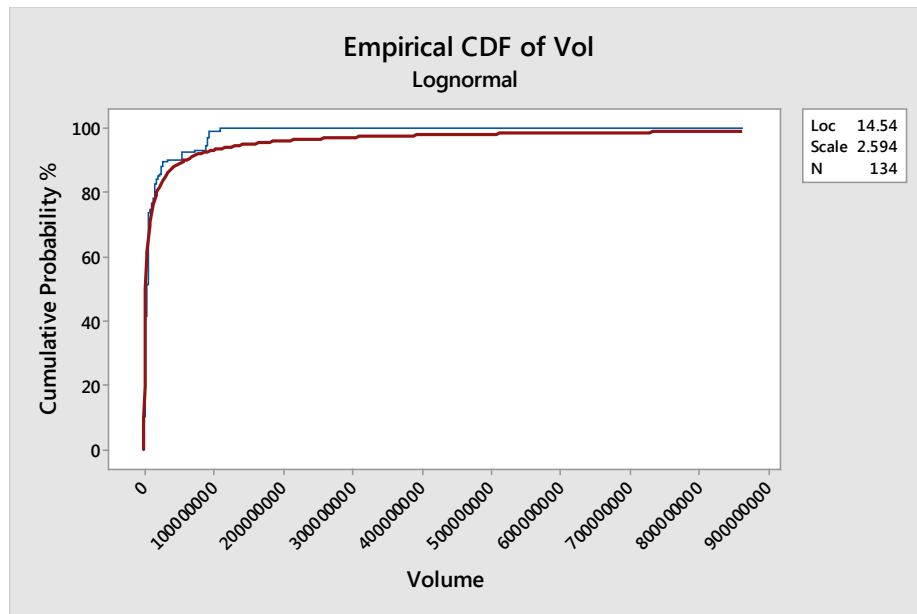


Figure 37: Cumulative Distribution Function for Volume

6.3.8 Product Complexity

Product complexity attribute measure several important features of the product such as product technology labeling, product manufacturing, and logistics features etc. Gathering information on these features on all products for quantification would be extremely difficult because such information does not exist in a database for all products. However, regulatory bodies or private entities can rely on their subject matter experts (or expert elicitation) to assess product complexities based on features discussed in this research. In this research, product complexity for each of product was determined because of the small amount of cases (n=134) that was available. Using Equation 6.12, the weights are determined for product complexity and are presented in Table 30.

$$P(PC_C | C) = \frac{\text{Number of counterfeit drugs by Product Complexity (c)}}{\text{Total Number of counterfeited drugs}} \quad \text{Equation 6.12}$$

Table 30 : Probabilities for Product Complexity

Product Complexity	Weight
Not Complex	4.48E-01
Complex	5.52E-01

6.3.9 Product Location

Product location represents where counterfeit drugs can be detected in the supply chain or where consumers can buy fake products. This attribute has two states: high and low risks. High risk locations considers where consumers has full access in getting medication from the internet (includes buying Rx or OTC products) and from entities that that hide under the radar from regulator bodies. A low risk location considers where counterfeit has the potential in infiltrating the supply chain if not detected and tested. They include wholesale (e.g. secondary), distributors or suppliers, pharmacies and customs etc. Using Equation 6.13, the probabilities are determined for product location and are presented in Table 31.

$$P(PL_r | C) = \frac{\text{Number of counterfeit drugs by Product Location } (r)}{\text{Total Number of counterfeited drugs}} \quad \text{Equation 6.13}$$

Table 31 : Probabilities Product Location

Product Location	Weight
High Risk	7.40E-01
Low Risk	3.60E-01

6.4 Results and Interpretation

The relationship between CFT Composite Score (CCS) and CFT Probability is proposed to estimate the probability of drug counterfeit. The CFT Composite Score (CCS) is derivation from the models proposed in section 6.2. The detail to derive a CCS score to CFT probability is depicted in Figure 36.

The derived relationship is depicted in Figure 37. The CFT probability measures were gathered from previous drug counterfeiting studies as discussed in chapters 4 and 5. For example, an estimated probability measure of 0.2 was determined for a certain drug product through analysis done by Health Authorities (20 products positive for counterfeiting out of 100 randomly sampled). Using the counterfeiting data collected by product, we can fit a relationship between CFT probability and CFT Composite Score to derive a model for converting CCS score to CFT probability.

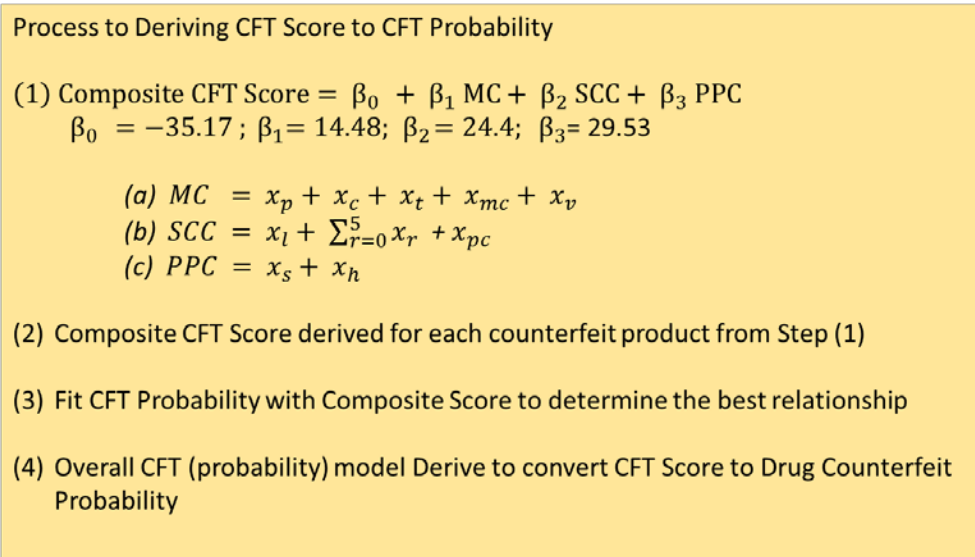


Figure 38: Process to Derive CFT Score to CFT Probability

Figure 38 depicts the best-fitted model based on the R-Square (adjusted) which is 26.00%. The overall CFT (probability) model is shown in Equation 6-14.

$$CFT (Probability) = 0.09280 + 0.008356 CCS + 0.008117 CCS^2 \text{ Equation 6-14}$$

Where:

CFT: Probability of Drug Counterfeit

CCS: Composite Score from Combined Models

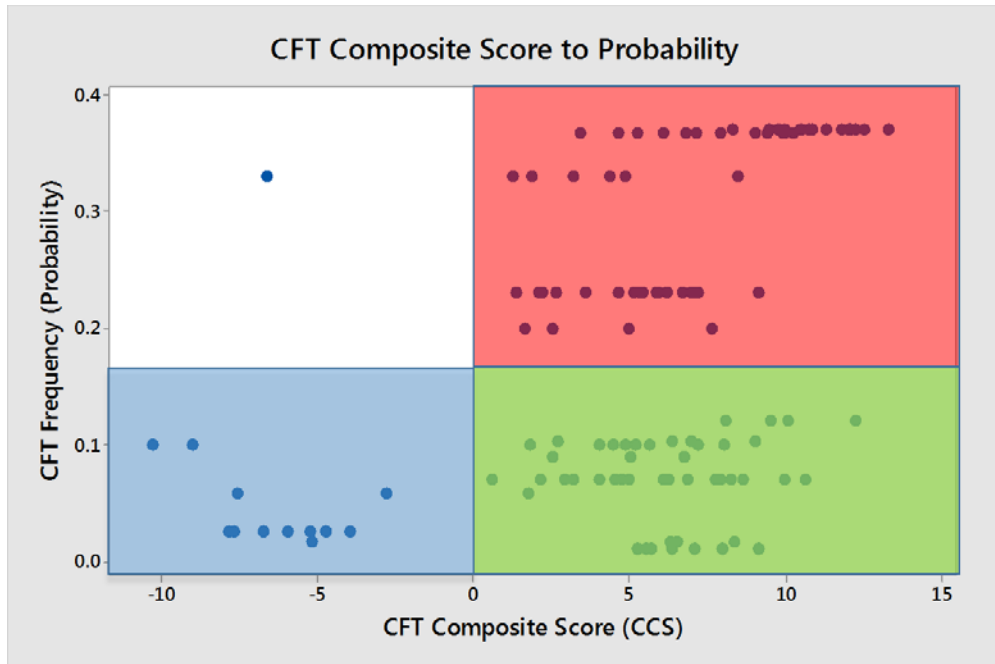


Figure 39: Composite CFT Scores to a Probability Measure

Through examination of the results, we see that there are three important regions: The Red, Green, and Blue zones each represent a degree or probability of drug counterfeiting.

- The red zone is a representation of drug products that are high risk of drug counterfeiting - high demand products with high unit price as well as low complexity of manufacturing, branded products, and importing from regions that have known history of product counterfeiting. Drug products having CFT scores ≥ 0 with probabilities ≥ 0.2 are red zone products.
- Drug products having CFT scores ≥ 0 with probabilities ≤ 0.2 are green zone products. These are high demand products with high unit prices as well as medium level complexity of manufacturing, and importing from regions that have

known history of product counterfeiting. Products in this region are majority branded products and prescription products

- Drug products in the blue zone are majority over-the-counter (OTC) products. Products in this region are purchased from internet sources. Thus, the model distinguishes among major categories of counterfeiting risk, which aids in planning counter measures.

Based on the relationship established we were able to assess the likelihoods of 13 counterfeit cases that occurred using the model produced from the fitted relationship produced in Figure 37. The results are depicted in Figure 38.

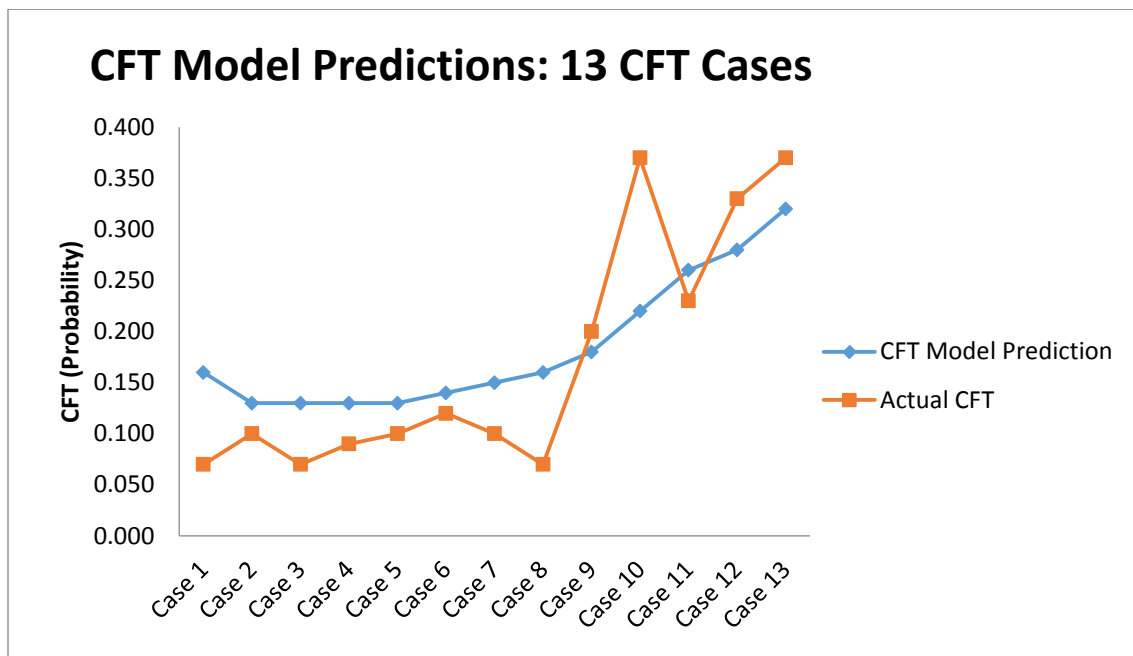


Figure 40 :13 Counterfeit Cases Predictions vs Actual Counterfeiting

Chapter 7: Model Uncertainty and Validation

7.1 Introduction

Model uncertainty analysis is essential to allow the identification at some level of confidence, the range of possible and probably values of the unknowns of interest. Our expression or knowledge of the unknown of interest is incomplete which implies uncertainty. Uncertainties may arise from researchers own assumptions and perceptions of the unknown of interest (Kazemi, 2011).

In this section, we will focus on model uncertainty using a Bayesian framework to improve the predictions of the CFT model. A Bayesian framework (Droguett & Mosleh, 2008) to update the predictive model is utilized to account for model error and provide a more reliable estimate using the CFT model presented in section 6.3.

Droguett and Mosleh (2008) presented their perspective on model uncertainty and discussed model uncertainty arises when we have the following:

- No plausible model,
- A single model, generally accepted, but not completely validated,
- Conceptually accepted and validated models, but of uncertain quality of implementation,
- A single model covering some but not all relevant aspects of the problem,
- Presence of multiple plausible models,
- Competing theories with contradictory predictions,

- Multiple models, each covering different aspects of the reality of interest, and
- Composite models formed from sub-models with different degrees of accuracy and credibility.

The uncertainty sources mentioned before (chapter 5) deal with values assumed by the model (parameter uncertainty) or the model itself (model uncertainty). Droguett and Mosleh (2008) developed two forms of models to deal with model uncertainty: Additive Error Model and Multiplicative Error Model discussed in section 7.2.

7.2 Framework

We are interested in assessing the true value of CFT , the likelihood of drug counterfeit. The counterfeit model's prediction is set as evidence, $E = \underline{CFT}^*$. The goal is to develop an uncertainty distribution of probability of counterfeit, CFT , given the evidence from the prediction of the counterfeit model developed in section 6.3. This uncertainty can be expressed as follows:

$$\pi(CFT | \overline{CFT}^*) = \frac{L(\underline{CFT}^* | CFT) \pi_0(CFT)}{\int_{CFT} L(\underline{CFT}^* | CFT) \pi_0(CFT) dcft} \quad \text{Equation 7.0}$$

where $\pi(CFT | \underline{CFT}^*)$ is the posterior distribution of drug counterfeit likelihood CFT , $\pi_0(CFT)$ is the prior distribution of CFT , and $L(\underline{CFT}^* | CFT)$ is the Likelihood of observing evidence \underline{CFT}^* when the true value for the likelihood of counterfeit of drug(s) CFT .

7.3 Multiplicative Error Likelihood Model

The multiplicative error model has several advantages over the additive model. Ontiveros and Modarres (2013) lists the common pitfalls of the additive model:

- Percentage error can be negative, zero, or positive; this forces the normal distribution assumption for the percentages errors;
- The choices of likelihood function is limits the random variable to normal distribution because of the percentage error (negative, zero, or positive);
- The distribution error between the model prediction and experiment cannot be analytically derived; and
- When data is widely scattered the normal distribution assumptions results in negative lower bounds with no meaningful physical interpretation.

The advantages of the multiplicative model are:

- Model predictions, result of the experiment, and real value of interest have the same sign (all positive or all negative);
- Ratio of the real value and experiments results is a random variable with lognormal distribution for which the confidence bounds are known;
- The distribution of the random variable is lognormal and will be used to represent the likelihood of the data; and
- The distribution of the real quantity [value] of interest given a model prediction will be a lognormal distribution.

An estimate obtained from the model is considered a random variable X^* , which is the product of the true but unknown value, x , and a random error, $X^* = x E$, in which X^* is the model estimate, x is the true value of the predicted variable, and E is a random multiplicative error. The realizations of the model, $\mathbf{x}^* (i=1, \dots, n)$ are then $\mathbf{x}_i^* = \mathbf{x}_i^t \mathbf{e}_i$, where \mathbf{x}_i^t and \mathbf{e}_i are realizations of the random variables X^* and \mathbf{E} , \mathbf{x}_i^t is the vector of true values of \mathbf{x} at i . Therefore, each realization of \mathbf{e}_i of \mathbf{E} is the quotient between the model's estimates \mathbf{x}_i^* and the true value at i , $\mathbf{e}_i = \mathbf{x}_i^* / \mathbf{x}_i^t$. Taking the logarithms, $\ln X^* = \ln x + \ln E$. Assuming that $\ln E$ is normally distributed, the Likelihood function become:

$$L(\mathbf{x}^* | \mathbf{x}, \boldsymbol{\theta}) = L(\mathbf{x}^* | \mathbf{x}, b, \sigma) = \frac{1}{\sigma \mathbf{x}^* \sqrt{2\pi}} e^{-\frac{1}{2} \left(\frac{\ln \mathbf{x}^* - (\ln \mathbf{x} + \ln b)}{\sigma} \right)^2} \quad \text{Equation 7.1}$$

in which $\boldsymbol{\theta} = \{b, \sigma\}$. This is log-normal with median (*i.e.*, bias factor) $b = E_{50}$, and standard deviation σ .¹

The posterior distribution for the set of parameters $\boldsymbol{\theta}$ is:

$$\pi(b, \sigma | e_1, \dots, e_n) = \frac{L(e_1, \dots, e_n | b, \sigma) \pi_0(b, \sigma)}{\iint L(e_1, \dots, e_n | b, \sigma) \pi_0(b, \sigma) db d\sigma} \quad \text{Equation 7.2}$$

Assuming the each pair of experimental and corresponding model estimates are independent realizations:

$$L(e_1, \dots, e_n | b, \sigma) = \prod_{i=1}^n L(e_i | b, \sigma) \quad \text{Equation 7.3}$$

¹ Commonly, the likelihood is written $L(\theta|x) = Pr(x|\theta)$. The Likelihood is defined over the support theta.

The form of the multiplicative error model is the following:

$$L(e_1, \dots, e_n | b, \sigma) = \prod_{i=1}^n \frac{1}{\sigma x^* \sqrt{2\pi}} e^{-\frac{1}{2} \left(\frac{\ln e_i - \ln b}{\sigma} \right)^2} \quad \text{Equation 7.4}$$

Substituting (7-5) into (7-2), we have the following representation:

$$\pi(b, \sigma | e_1, \dots, e_n) = \frac{1}{k_1} \prod_{i=1}^n \frac{1}{\sigma} e^{-\frac{1}{2} \left(\frac{\ln e_i - \ln b}{\sigma} \right)^2} \pi_0(b, \sigma) \quad \text{Equation 7.5}$$

where $k_1 = \iint \prod_{i=1}^n \frac{1}{\sigma} e^{-\frac{1}{2} \left(\frac{e_i - b}{\sigma} \right)^2} \pi_0(b, \sigma) db d\sigma$ is a normalizing constant and $\pi_0(b, \sigma)$ is the prior distribution on b and σ .

7.4 Drug Counterfeit Model Uncertainty

Adapting the above formulation, the Likelihood for the drug counterfeit model becomes,

$$L(CFT^* | CFT, b_{cft}, \sigma_{cft}) = \frac{1}{\sigma_{cft} CFT^* \sqrt{2\pi}} e^{-\frac{1}{2} \left(\frac{\ln CFT^* - (\ln CFT + \ln b_{cft})}{\sigma_{cft}} \right)^2} \quad \text{Equation 7.7}$$

in which, $b_{cft} = E_{50}$ is the median of the error distribution, and σ_{cft} is the standard deviation. The posterior PDF of the parameters b_{cft}, σ_{cft} is:

$$\pi(b_{cft}, \sigma_{cft} | \varepsilon_1, \dots, \varepsilon_n) = \frac{L(\varepsilon_1, \dots, \varepsilon_n | b_{cft}, \sigma_{cft}) \pi_0(b_{cft}, \sigma_{cft})}{\iint L(\varepsilon_1, \dots, \varepsilon_n | b_{cft}, \sigma_{cft}) \pi_0(b_{cft}, \sigma_{cft}) db_{cft} d\sigma_{cft}} \quad \text{Equation 7.8}$$

where $\pi_0(b_{cft}, \sigma_{cft})$ is the prior distribution of b_{cft}, σ_{cft} and $\{\varepsilon_1, \dots, \varepsilon_n\}$ is a vector of calibration data.

The posterior distribution of the likelihood function parameters is:

$$\pi(b_{cft}, \sigma_{cft} | \varepsilon_1, \dots, \varepsilon_n) = \frac{1}{k} \prod_{i=1}^n \frac{1}{\sigma_{cft}} e^{-\frac{1}{2} \left(\frac{\ln e_i - \ln b_{cft}}{\sigma_{cft}} \right)^2} \pi_0(b_{cft}, \sigma_{cft}) \text{ Equation 7.9}$$

where $\pi_0(b_{cft}, \sigma_{cft})$ is the prior distribution of b_{cft}, σ_{cft} , and k ;

$$k = \iint \prod_{i=1}^n \frac{1}{\sigma_{cft}} e^{-\frac{1}{2} \left(\frac{e_i - b_{cft}}{\sigma_{cft}} \right)^2} \pi_0(b_{cft}, \sigma_{cft}) db_{cft} d\sigma_{cft} \text{ Equation 7.10}$$

The likelihood of the new counterfeit prediction model becomes the following:

$$\begin{aligned} L(CFT^* | \text{performance data}, CFT) \\ &= \iint \frac{1}{\sigma_{cft} CFT^* \sqrt{2\pi}} e^{-\frac{1}{2} \left(\frac{\ln CFT^* - (\ln CFT + \ln b_{cft})}{\sigma_{cft}} \right)^2} \\ &\times \frac{1}{k} \prod_{i=1}^n \frac{1}{\sigma_{cft}} e^{-\frac{1}{2} \left(\frac{\ln e_i - \ln b_{cft}}{\sigma_{cft}} \right)^2} \pi_0(b_{cft}, \sigma_{cft}) \end{aligned}$$

$$\begin{aligned} L(CFT^* | \text{performance data}, CFT) = \\ \iint \frac{1}{\sigma_{cft} \sqrt{2\pi}} e^{-1/2 \left(\frac{CFT^* - (CFT + b_{cft})}{\sigma_{cft}} \right)^2} \times \frac{1}{k} \prod_{i=1}^n \frac{1}{\sigma_{cft}} e^{-1/2 \left(\frac{\varepsilon_i - b_{cft}}{\sigma_{cft}} \right)^2} \pi_0(b_{cft}, \sigma_{cft}) \\ db_{cft} d\sigma_{cft} \end{aligned} \text{ Equation 7.11}$$

The new posterior of the counterfeit prediction model becomes the following:

$$\pi(CFT | CFT^*, \varepsilon_1, \dots, \varepsilon_n) = \frac{1}{k} L(CFT^*, \varepsilon_1, \dots, \varepsilon_n | CFT) \pi_0(CFT) \text{ Equation 7.12}$$

Where k , is a normalizing constant.

7.5 Bayesian CFT Model Uncertainty Analysis and Validation

To validate the model; we updated the 13 counterfeit cases that were presented in this section and included 10 new cases studies that were not counterfeited. The procedure to validate the counterfeit drug model is depicted in Figure 39.

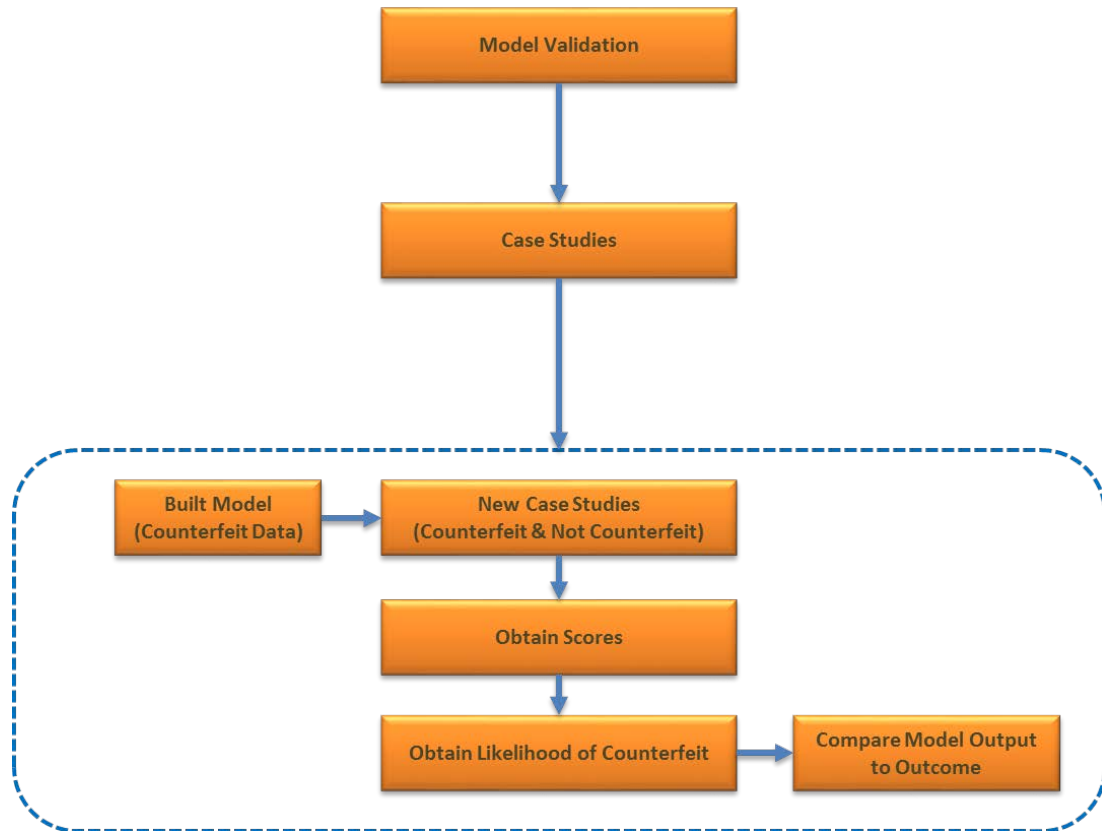


Figure 39: Validation Procedure for Drug Counterfeit Model

7.5.1 Bayesian Updates

Using 120 counterfeit cases, we can now apply the framework to improve our model predictions. The 120 counterfeit cases are the performance data used to calibrate the model. Then we used 13 additional counterfeit cases, which had been removed from the data set, to demonstrate that with updating the model with new case(s), the model prediction (performance) improves. In other words, as we update the model with additional cases ($N = 120, N+1, N+2, N + \dots$), the performance of the model prediction for each counterfeit case improves.

The Bayesian computations were done using the “The Model Uncertainty Software” created by the Center for Risk and Reliability Engineering at the University of Maryland, College Park, in 2006 and is available at that center, following the procedure of Section 7.4.

Figure 40 depicts (for one case) the distribution of the posterior function of the prediction for drug counterfeiting taking into account the performance of the CFT prediction model. The graph in Figure 40 depicts one counterfeit case prior and after Bayesian updating using performance data. Prior to using the performance data to update, we see that the CFT model predicted the probability of drug counterfeit as 0.163. After updating the model with the performance data, we see that the model new prediction (posterior mean) is 0.144 with the actual product counterfeit being 0.10. We see that the prediction improved using the Bayesian method. Using the Bayesian method, the results of our new model predictions are depicted in Table 32. The model predictions improved by 14%; the

original CFT predictions error was approximately 33%, with the Bayesian updating it was 19%.

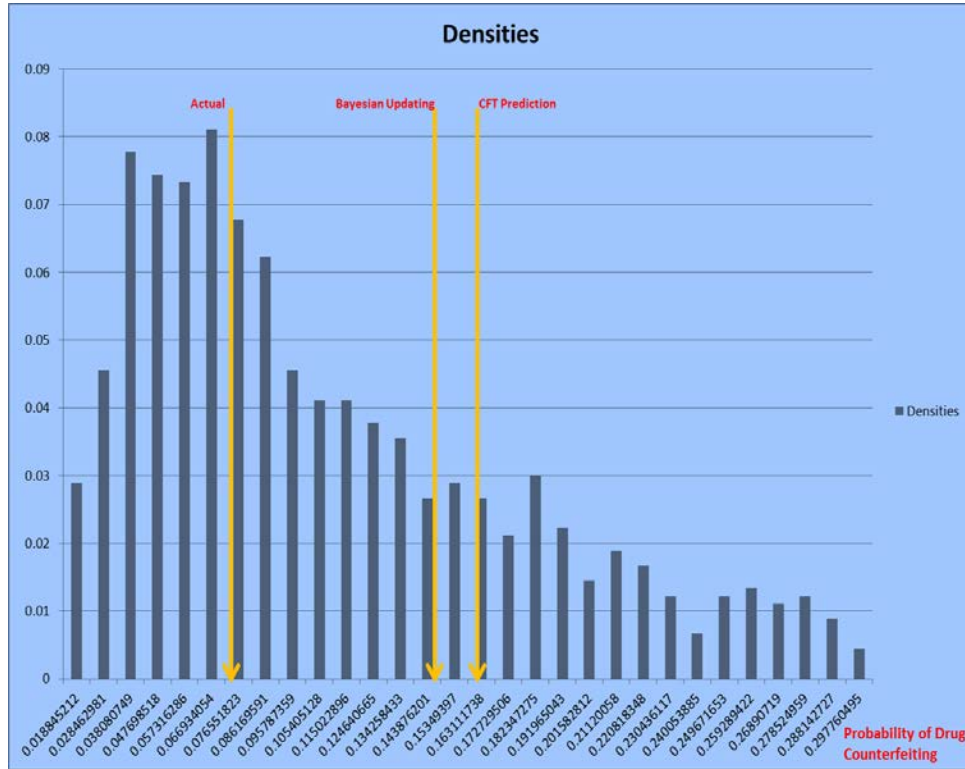


Figure 40: Posterior Distribution of Probability of CFT via Bayesian Model Uncertainty Method

Table 32 : Counterfeit Cases Predictions with Bayesian Updating

CFT Cases	CFT Model Prediction	Bayesian CFT Updating	Product CFT
Case 1	0.160	0.158	0.070
Case 2	0.130	0.079	0.100
Case 3	0.130	0.095	0.070
Case 4	0.130	0.070	0.090
Case 5	0.130	0.081	0.100
Case 6	0.140	0.101	0.120
Case 7	0.150	0.140	0.100
Case 8	0.160	0.144	0.070
Case 9	0.180	0.209	0.200
Case 10	0.220	0.310	0.370
Case 11	0.260	0.250	0.230
Case 12	0.280	0.382	0.330
Case 13	0.320	0.404	0.370

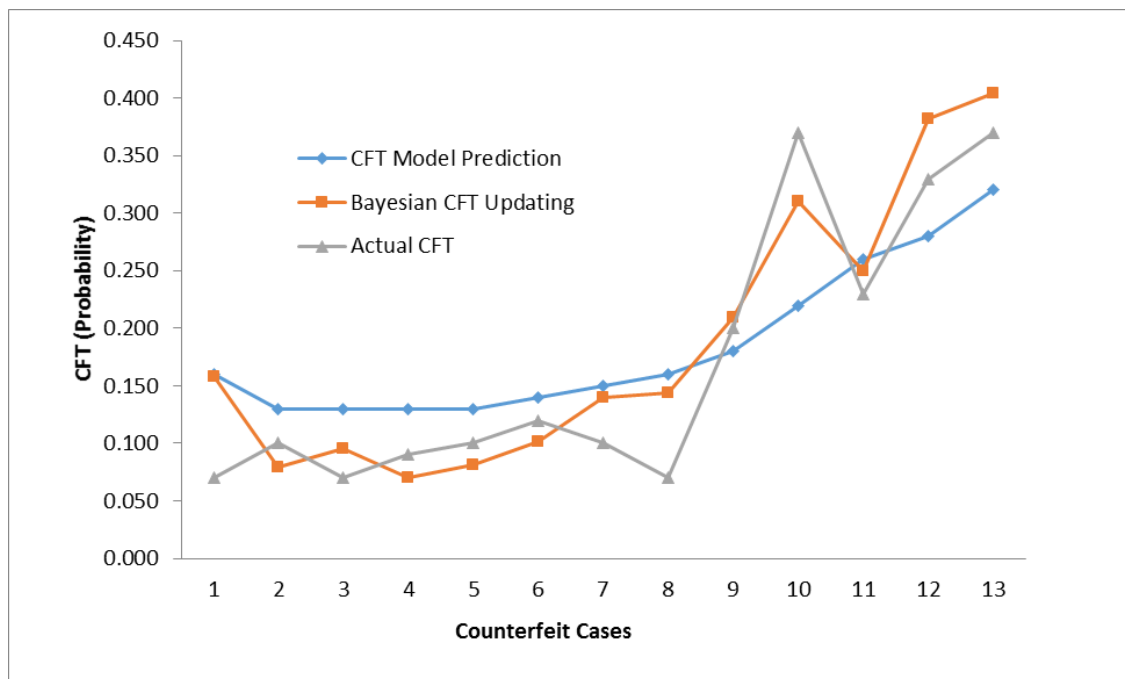


Figure 41: Bayesian CFT Updating Results

The results shown in Figure 41 represent the 13 counterfeit case after calibrated with the Bayesian method. Using the performance data ($n = 120$), each case was ran independently and the probabilities presented in graph above represent the posterior mean of each counterfeit case.

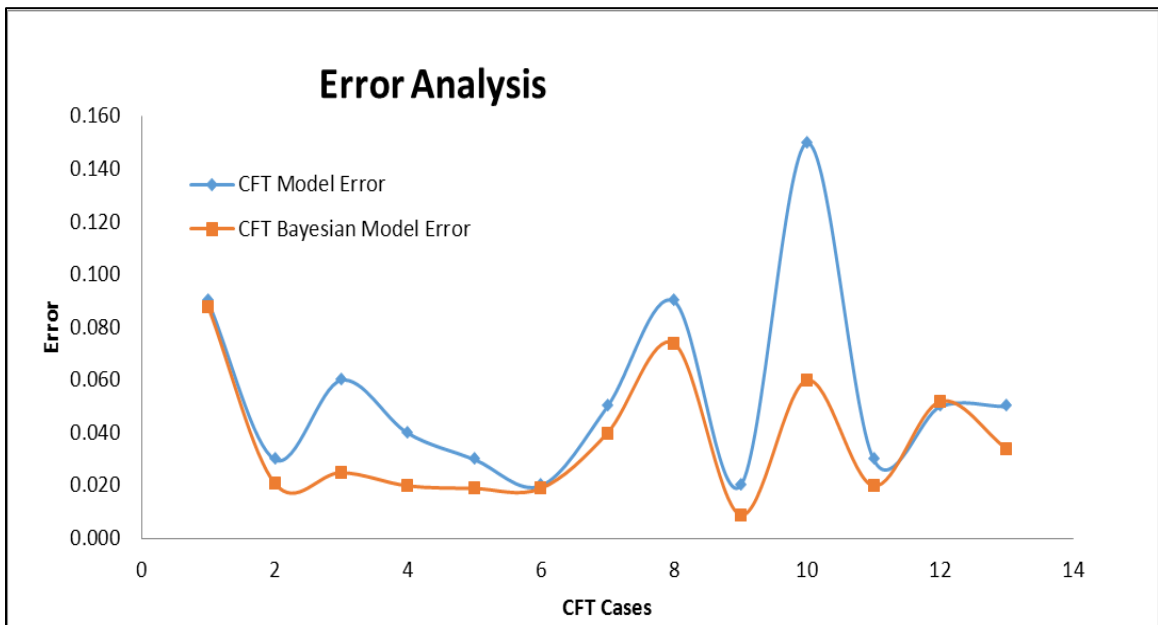


Figure 41: Models Errors: CFT Model and CFT Bayesian

Figure 41 compares the error for each individual counterfeit case after calibration. We see that the model performance improves with each case.

7.5.2 Model with Cases Not Counterfeited

To validate the model with drugs that are less likely to be counterfeited will ensure that model predictions are reliable enough to accept the outcomes. To do so, one compliance regulatory expert was asked to provide 10 cases of drugs that are less likely to be counterfeited as well as asked to rank the product complexity (complex or not complex) using the criteria's provided in this research. The results of the 10 cases are depicted in Figures 42, 43 and Table 33. The results obtained from the model predictions depict small likelihoods of drug counterfeiting.

Table 33 : Test Cases Outcome with Bayesian Updating Method

Cases	CFT Model Prediction	CFT Bayesian Prediction
Case 1	0.035	0.026
Case 2	0.030	0.015
Case 3	0.074	0.031
Case 4	0.078	0.034
Case 5	0.085	0.041
Case 6	0.075	0.033
Case 7	0.082	0.038
Case 8	0.086	0.056
Case 9	0.070	0.030
Case 10	0.068	0.030

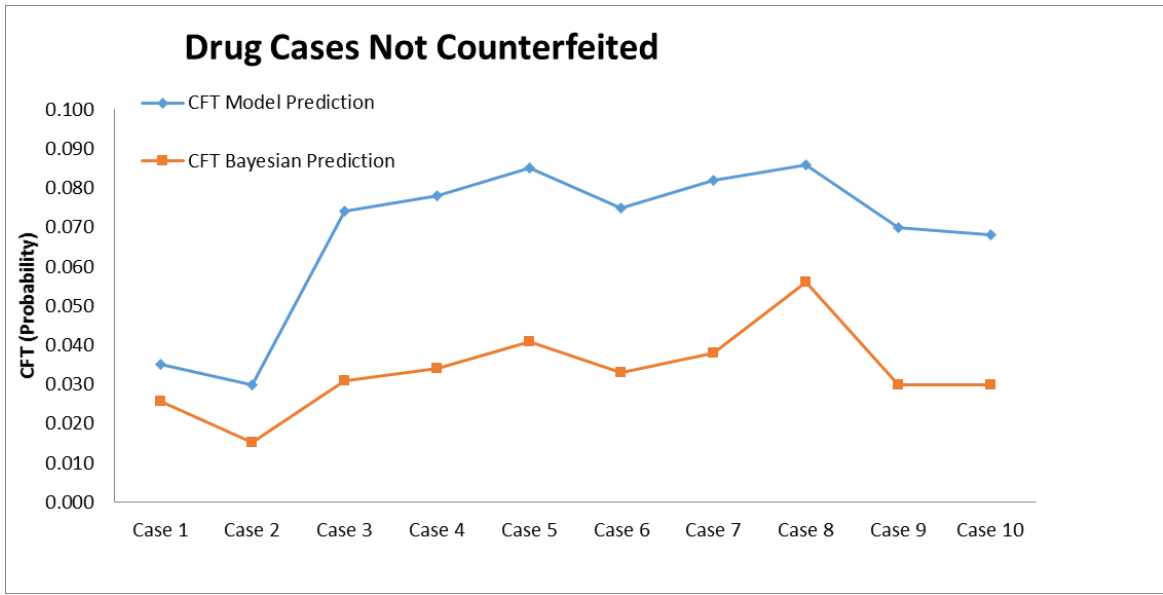


Figure 42: Low Risk of Counterfeiting Model Predictions

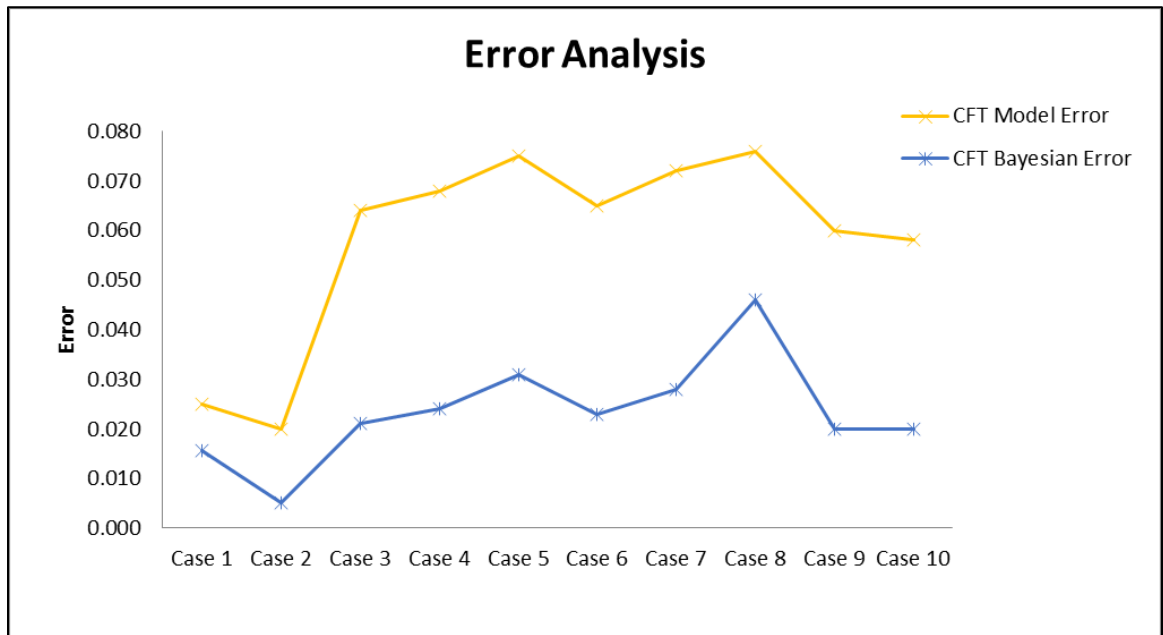


Figure 43: Error Analysis for Low Risk of Counterfeiting

The results provided by the model predictions are low probabilities of counterfeiting compared to cases that were counterfeited. Figure 42 depicts the model predictions are not erroneous. Each case selected by the regulatory expert had small probabilities of counterfeiting because of drug tight controls around the drug manufacturing process, low demand and complex technologies to produce the drug.

Chapter 8: Research Findings, Conclusions, and Recommendations

8.1 Introduction

This chapter discusses the research findings, conclusions and implications of these finding for preventing drug counterfeiting in the pharmaceutical industry.

By using factor and regression analyses, three distinct counterfeit factors emerged: Market Characteristic, Product History Characteristics, and Supply Chain Characteristics. Taking into account these three factors, decision makers can assess products in an objective and robust way to determine which products are greater risk of counterfeiting and develop policies and strategies to mitigate or minimize counterfeit drugs in the legitimate supply chain.

8.2 Public Health

Globalization has served as a catalyst for counterfeiters to exploit and profit from weak regulations and complexities in the pharmaceutical supply chain (i.e., buying fake products online). Under this scenario, there are more reports of counterfeit products finding their way into the homes of consumers. Deaths and illnesses related to counterfeits drugs continue to grow.

The findings and the model created in this dissertation could benefit private entities and drug regulators in numerous ways:

- With the growing number of counterfeit products entering the supply chain; regulators for example cannot spread limited resources to every point in the pharmaceutical supply chain. This research provides a method to rank drug products based on their likelihoods of counterfeiting. This enables private entities and regulators to focus on products in a smarter way for sampling and testing.
- Using the drug counterfeit model with statistical sampling tool could help private and regulatory bodies to develop robust sampling plans to test the supply chain. A statistical sampling plan is a cost effective method for determining how many products to sample after it is determined which products should be under surveillance. In addition, a sampling plan is useful when there are potentially serious product risks (e.g., counterfeiting) (Montgomery, 2001). Sampling plans such as ABC-STD-105 which is based on MIL-STD-105D developed by the United States Military in 1963 can be utilized to develop different strategies for sampling and testing.
- Develop strategies to target high risk regions where products tend to originate.

8.3 Supply Chain

The rise in terrorist activities has also affected the drug supply chain (Deloitte, 2014). In particular, the Internet has been and will be a catalyst for criminals to introduce counterfeit products into the legitimate supply chain. The majority of online pharmacies have locations around the globe and they are unregulated or lack proper credentials to engage in the distribution of drugs (Liang & Mackey, 2012). This research highlighted that counterfeit drugs can be purchased through the internet by consumers not knowing the real risk. This model utilized supply chain characteristics factor to help decision makers identify potential avenues counterfeit drugs can infiltrate the market without detection. The traditional pharmaceutical supply chain is becoming more complex with the digital age; therefore, it is imperative that much more focus be placed on the “cyber-pharmaceutical-supply-chain.”

8.4 Future Landscape - Drug Shortages Increasing Trend

Drug shortages, an attribute not considered in previous studies was introduced in this research and is considered an important element. Although, the overall product profile characteristic was not statistically significant, this factor must be considered because when drug shortages occurs, physicians, hospitals, and patients explore options such as purchasing drugs online (Liang & Mackey, 2011). This creates an opportunity for counterfeiters to introduce poor quality or counterfeit drugs into the legitimate supply chain. This research recommends the inclusion of drug shortages and past counterfeiting attributes data into the decision-making process to develop policies for mitigating and minimizing the risk of counterfeiting drugs reaching consumers. Specifically, in assessing

the likelihood of counterfeiting, there should be a determination about which product(s) can be sold over the internet, and strategies developed to target and sample products as well as to develop appropriate risk communication tools.

In addition, this study indicates that whenever a pandemic occurs, this model should be used to determine which products or substitute products are at risk for being counterfeited, and develop dynamic surveillance systems to educate the public of the potential health risk. For example, during the H5N1 influenza outbreak, FDA and the Dutch Healthcare Inspectorate issued warning regarding fake anti-viral drugs sold online (WHO, 2006).

8.5 Conclusions

Drug counterfeiting is on the rise. Limited empirical research is available on drug counterfeiting, specifically factors and models to assess counterfeiting likelihoods. This research could help private and public entities mitigate and minimize counterfeit drug reaching consumers.

This research aimed to be exploratory by conducting a thorough analysis of counterfeit factors and by developing a model to assess the likelihood of counterfeiting. The findings of this research have led to these substantive outcomes:

- **Key counterfeit attribute have been identified:** 10 counterfeit attributes were identified: Average Price, Drug Class, Medication Class, Product Type, Volume, Product Complexity, Product Location, Region, Previous Product Counterfeiting,

and Product Shortage - through literature reviews, case studies, and experts. These combined in three explanatory factors: MCC, PPC, and SCC.

- **A data-driven conceptual model has been developed for drug counterfeit built from data:** Through the use of exploratory factor analysis, a model emerged with above three distinct factors. Through regression analysis, market and product history factors were shown to be statistically significant for assessing drugs counterfeiting risk.
- **A process and a model to determine probability of drug counterfeiting has been developed.** This is first time a process and model has been developed to assess the probability of drug counterfeiting. This process and model can aide decision makers in ranking drug inventory for inspection and sampling purposes.

8.6 Research Limitations

This research is the first type to explore drug counterfeit factors and developed a model to assess likelihood of drug counterfeiting. However, as with all research, there are limitations. Some of the limitations of this research are:

- A limited set of counterfeit data was used to study counterfeit factors. A larger number of data may have strengthened the findings in this study.
- A limited set of experts was used. More experts should be included to gain confidence on the counterfeit attributes. Including more experts may have strengthened the findings.
- All of the counterfeiting data used in this study came from pharmaceutical cases. Other industries such as aerospace also suffer from product counterfeiting. Data

should be included counterfeit data from these other industries to enriching the results.

8.7 Recommendations

The primary focus of this research was to explore factor significance on drug counterfeiting and to develop a model to determine the probability of drug counterfeiting.

Future research could include the following:

- Conduct a confirmatory factor analysis method on the 10 counterfeit attributes and three counterfeit factor derived in this study. This could be done via survey to include government and industry experts.
- Explore the use of Bayesian Belief Networks to model and determine the likelihood of drug counterfeiting.
- Explore developing a consequence model (or analysis) to determine the impact of pharmaceutical counterfeiting event on patient safety. This research explores on the probability (or likelihood) of pharmaceutical counterfeiting.

8.8 Guide Map for the Government and Private Industries

This research highlight the need to have consistent definition among regulatory bodies for drug counterfeiting and a need for a global drug counterfeit database to conduct analysis and drug surveillance. In addition, supply chain guidelines should be used with the model developed in this research. Therefore the following could be implemented:

- Develop a global definition of drug counterfeiting;
- Develop a counterfeit database to enable legitimate users to enter counterfeit information; the counterfeit attributes presented in this study could be useful to develop the first database; and
- Use the drug counterfeit model to assess and rank regulated drug inventories on a monthly basis to determine which products should be under surveillance. Focus on high risk locations first (e.g., internets and imports) may be beneficial.

Appendix A

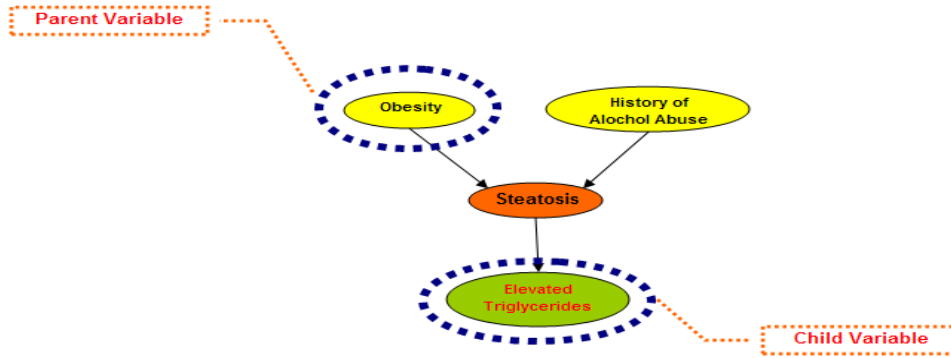
Modeling the Likelihood of Product Counterfeit

Conceptual Drug Concept Influence Diagram Interviewing Experts

Introduction

Influence diagram a generalization of a Bayesian Network and can incorporate probabilistic relationships between variables, as well as past and current information about their relationships. They are extremely useful for modeling scenarios where some information is already known and incoming data is uncertain or not available. These networks offer consistent semantics for representing cause and effect (and likelihoods) via an intuitive graphical representation. The Figure below depicts a simple example of a Bayesian network, i.e., there is an influence of Obesity on Steatosis. Influences are represented by connecting influencing variables (parent variables) to influenced variables (child variables).

The nodes are variables, and the links represent dependencies or casual influences. The links allow mapping of dependence relationship between variables and the strength of the relationships is expressed by forward conditional probabilities. Each node has a conditional probability table that quantifies the effects of the parents on the child node.



Expert Information

Name: Optional

Years of Experience:

Organization Type: Private or Public

What is your professional/educational background:

Model Validation

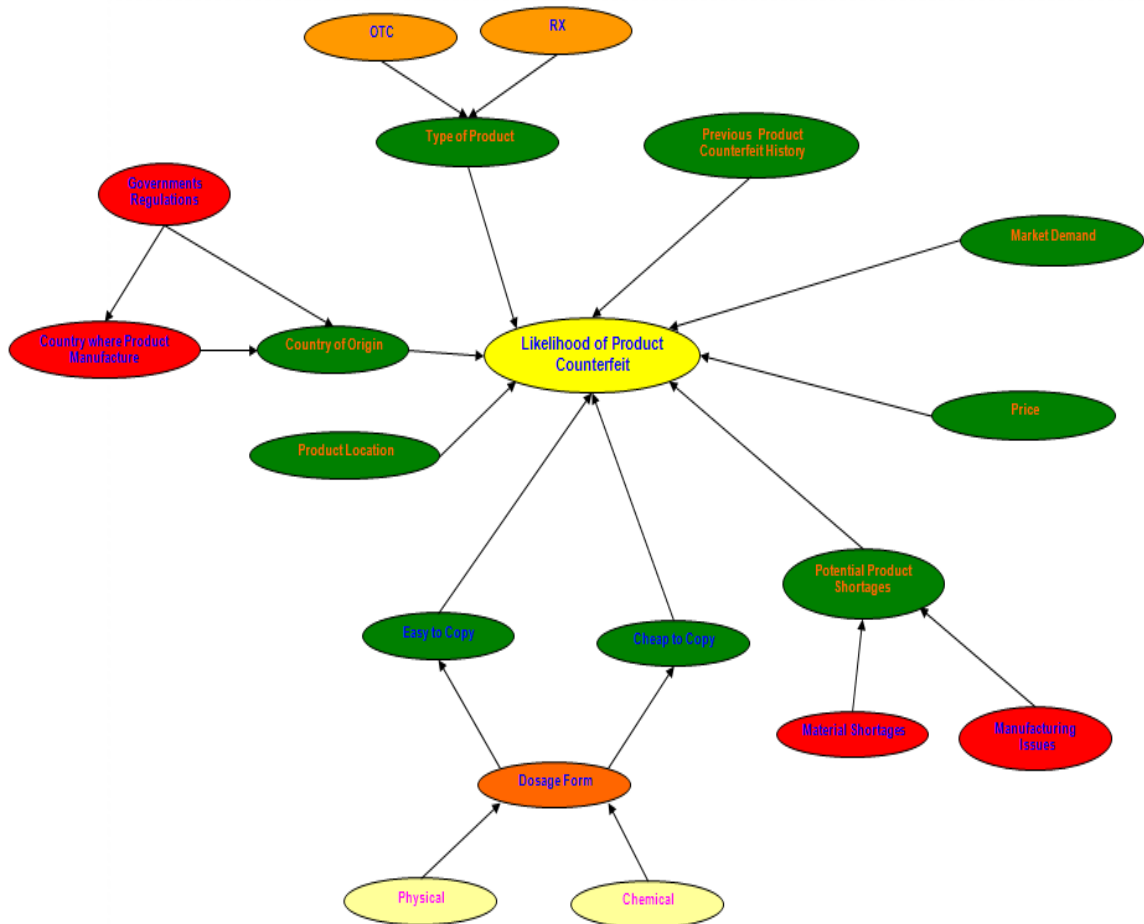
Regarding Detecting the Likelihood Counterfeiting of Drugs:

1. From your perspective what are the most important factors that influence the risk of drug counterfeiting in the US?

Evaluation of Model

Examine the influence diagram (BBN) provided. Based on the influence diagram you provided, let's fill in parts that you mentioned, and also are missing from this model.

[Interviewer will iteratively work with the interviewee/subject to incorporate or exclude specific variables from the base model]



Evaluation for Expert

Completeness: From your perspective, to what extent does this model capture all important and relevant phenomena for the particular problem under study? On a scale 0 to 100, 0 would correspond to a model that does not include some important and relevant details, where as 100 would correspond to a model that includes all the details you consider important:

Accuracy: From your perspective, how accurately or realistically does the model depict important facts that predict the risk of pharmaceutical being counterfeited? On a scale from 0 to 100, 0 would correspond to a model that is unrealistic or inaccurate, while a 100 would correspond to a model is realistic and accurate:

Ease of Understanding: From your perspective, how easy it is to understand the overall logic of the model. On a scale from 0 to 100, 0 would correspond to a model that is difficult to follow, and a 100 would correspond to a model that is readily understandable:

Additional Comments

If something was not discussed during this meeting, please do not hesitate to contact me.

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