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DRUG SUPPLY CHAIN SECURITY ACT OF
2013 AND ITS COMPUTER SYSTEM
IMPLEMENTATION

A Thesis
Presented To
Eastern Washington University
Cheney, Washington

In Partial Fulfillment of the Requirements
for the Degree
Master of Business Administration

By
Daryl O. Jones
Summer 2014

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MASTER'S THESIS

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Abstract

Since 1987, the federal government and state governments, have tried to combat counterfeit drugs from entering the United States and the states' pharmaceutical supply chain. The latest attempt to prevent counterfeit drugs from entering the state drug supply chain was the California E-Pedigree drug tracing program that was to be implemented by the end of 2017. The California E-Pedigree system uses GS1 PDMS tracing system as its guideline. Since all of the states use paper format pedigree systems, California would have been the first electronic pedigree system in the U.S.

However, on November 27, 2013, the President of the United States signed into law the Drug Quality Security Act (DQSA). Title II of DQSA is called the Drug Supply Chain Security Act (DSCSA) and it removes all existing or future drug track or trace systems including pedigree systems from all states. DSCSA does establish a new federal drug tracing program that uses pedigrees and product identifiers for verification of the drugs being accepted by the buyer. Although the full implementation of the DSCSA will take about ten years from its enactment, the basic structure of the new federal tracing program is laid out.

My thesis will analyze the current state of the pharmaceutical industry, the impact of counterfeit medicine, and anti-counterfeit technologies. We will proceed to analyze the DSCSA to create a basic logical model and show a possible implementation of its verification process. Additionally, we will discuss DSCSA model as to its effectiveness of the basic design against the entrance of counterfeit medicine into the United States Pharmaceutical Supply Chain. This will be followed by a conclusion.

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1. Introduction

This thesis is an analysis and prospective implementation of the current federal tracing drug program, Title II of the Drug Quality and Security Act (DQSA) which is referred to as Drug Supply Chain Security Act (DSCSA), that was passed by Congress and signed into law by the president on November 27, 2013. DSCSA was created to consolidate the many current state drug tracing programs and future efforts to reduce counterfeit medicine from entering the United States pharmaceutical supply chain (USPSC). To understand the need for such a program, we need to appreciate the current state of the pharmaceutical industry, the impact from counterfeit medicine, and the anti-counterfeit technologies being employed.

We analyze the pharmaceutical industry's revenues and cost, define the term "counterfeit medicine," and show the cost of the counterfeit medicine on the pharmaceutical industry, governments, and citizens. We conduct a high level review of anti-counterfeit technologies which ends with the new federal tracing program, DSCSA. We analyze the new law and come up with a basic logical model of the new trace program by providing logical flow charts, ERD diagrams, and product identifier verification implementation. We discuss the effectiveness of the new drug tracing program against known counterfeit drug intrusions and come to a conclusion.

Why is the subject important? Drug counterfeiting reduces the global pharmaceutical industry's revenues (Davison, 2011; World Health Organization, 2008), which in turn has an effect on new drug development in terms of costs and productivity (Davison, 2011). In addition, counterfeit drugs have human, corporate, and governmental costs (Davison, 2011). These adverse consequences eventually affect all of us in terms of increased rates in our

medical co-payments, insurance rates, and taxes. These detrimental effects are not only found in undeveloped nations but are found in an alarming rate in developed nations (J. Morris & Stevens, 2006; Wertheimer & Wang, 2012). In addition, organized crime is involved at all levels of drug counterfeiting (Davison, 2011; UNICRI, 2013; Wertheimer & Wang, 2012).

First we analyze the global pharmaceutical industry's (GPI) revenues and costs and then follow with an analysis of the United States pharmaceutical industry's revenues and costs. Next, we do a review of counterfeit drugs, definition, costs, reasons for counterfeiting, and the involvement of organized crime. This is followed by a quick review of the anti-counterfeit technologies which include authentication and product track-and-tracing. We cover the DSCSA law which provides a basic framework for the new federal drug tracing system and by produce a logical model by first analyzing the DSCSA's definition, structure, and requirements. From this logical model, we can review the effectiveness of the new federal tracing program and come to some conclusions.

2. Literature Review

This section is a literary review of the current state of the pharmaceutical industry, counterfeit medicine, anti-counterfeit technologies, and the challenges they create. As indicated from this literary review, counterfeit medicine is a large problem for the global pharmaceutical industry but the problem is much larger in the underdeveloped (30%-50%) nations than the developed (1%-3%) nations (World Health Organization, 2008). To explain the effects of counterfeit medicine, we look at the current global pharmaceutical industry revenues and costs. Next, we look at the current costs of counterfeit medicine and organized crime involvement in counterfeit medicine. Lastly, we search the literature to find the latest anti-counterfeit drug technologies.

To understand these challenges, we need to appreciate at a high level the issues of GPI revenues and their costs. An additional appreciation is needed on the cost of counterfeit drugs. We need to recognize how counterfeit drugs are entering the global supply chain and the USPSC. Furthermore, we need to comprehend the current anti-counterfeit drug technologies.

First, let's look at the pharmaceutical revenues because without an easy profit to be made by the counterfeiters, there would not be any counterfeit drugs (Davison, 2011; UNICRI, 2012; Wertheimer & Wang, 2012). To follow revenue, we need to cover the cost of producing a drug that is sold on the market and the productivity issues. We then cover the cost of counterfeiting and how counterfeit drugs are entering the USPSC. Lastly, the anti-counterfeit technologies will be covered.

All dollar amounts are in United States currency unless stated otherwise.

2.1 Pharmaceutical Industry Revenues

Using the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) report for 2011, Annex 3 data, the total global pharmaceutical sales revenues for 2011 was calculated to be over \$1,086 billion (International Federation of Pharmaceutical Manufacturer & Associations, 2012). IFPMA stated that in 2011 the United States had the largest market, with 31% percent of the global sales market (International Federation of Pharmaceutical Manufacturer & Associations, 2012). The next biggest market was Japan, followed by China, Germany, and France. (see Table 1)

Table 1 PHARMACEUTICAL SALES (2011)

Rank	GEOGRAPHY	US\$BN	Percent of Market
1	United States	\$ 337.10	31.02%
2	Japan	\$ 127.38	11.72%
3	China	\$ 66.86	6.15%
4	Germany	\$ 55.15	5.07%
5	France	\$ 48.66	4.48%

Source: The Pharmaceutical Industry and Global Health: Facts and Figures 2012

Retrieved: 3/15/2014

Pharmaceutical Executive reported in 2013 that the top 50 global pharmaceutical companies have total product revenues over \$594 billion (Noor, May 1, 2013). The top five companies are Pfizer, Novartis, Merck & Co., Sanofi, and Roche for a total over \$209 billion. The top ten had a total over \$335 billion. (see Table 2)

Table 2 2013 PharmExec Top Ten

No.	Company	Company HQ	RX Sales (US\$Bn)	
1	Pfizer	USA	\$	47.404
2	Novartis	Switzerland	\$	45.418
3	Merck	USA	\$	41.143
4	Sanofi	France	\$	38.370
5	Roche	Switzerland	\$	37.542
6	GlaxoSmithKline	UK	\$	33.107
7	AstraZeneca	UK	\$	27.064
8	Johnson & Johnson	USA	\$	23.491
9	Abbott	USA	\$	23.119
10	Eli Lilly	USA	\$	18.509
		Total	\$	335.167

Source: The 2013 Pharm Exec Top 50

Retrieved: 6/10/2014

My further investigation of the data and calculations reveals seventeen companies out of the top 50 are United States companies that have aggregate sales revenues over \$232 billion. Switzerland had three companies with an aggregate sales revenues over \$87 billion making it number two on the list. Japan had 10 companies with aggregate sales revenues over \$68 billion. United Kingdom follows with aggregate sales revenue over \$60 billion. Germany had five companies with aggregate sales revenues over \$41 billion.

According to IMS Health, global pharmaceutical revenues have been increasing for decades, except for a decrease from 2011 to 2012 from \$964.8 to \$962.1, a loss of \$2.7 billion (IMS Health Incorporated and its affiliates, 2013b). (see Table 3)

Table 3 Total Unaudited and Audited Global Pharmaceutical Market

Total World Market	
Year	Billions
2012	\$962.10
2011	\$964.80
2010	\$891.30
2009	\$834.40
2008	\$801.40
2007	\$729.30
2006	\$657.80
2005	\$611.00
2004	\$564.50
2003	\$502.20

Note: US\$ uses actual quarterly exchange rates

Source: IMS Health Market Prognosis, June 2013

Retrieved Date: 3/17/2014

The United States pharmaceutical market reported a loss of revenue from 2011 to 2012 of \$3.4 billion (IMS Health Incorporated and its affiliates, 2013a). (see Table 4)

Table 4 Total US market Non-Discounted Spending

Year	US\$Bn
2012	\$325.80
2011	\$329.20
2010	\$316.50
2009	\$300.70
2008	\$285.70

Source:

http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Corporate/Press%20Room/2012_U.S./Top_Companies_by_Non-Discounted_Spending_U.S.pdf

Retrieved: 3/17/2014

In 2013, eight out of the top twenty global pharmaceutical firms experienced a drop in sales from 2012 (IMS Health Incorporated and its affiliates, 2014). (see Table 5)

Table 5 TOP 20 GLOBAL CORPORATIONS 2013

2013 RANK	Company	(US\$ Mn)		
		2013 SALES	2012 SALES	Sale Diff.
1	NOVARTIS	\$ 50,576	\$ 50,521	\$ 55
2	PFIZER	\$ 44,330	\$ 46,707	\$ (2,377)
3	SANOFI	\$ 38,181	\$ 38,531	\$ (350)
4	MERCK & CO	\$ 36,350	\$ 39,891	\$ (3,541)
5	ROCHE	\$ 36,146	\$ 34,958	\$ 1,188
6	GLAXOSMITHKLINE	\$ 32,544	\$ 32,736	\$ (192)
7	JOHNSON & JOHNSON	\$ 30,784	\$ 27,717	\$ 3,067
8	ASTRAZENECA	\$ 30,257	\$ 31,704	\$ (1,447)
9	TEVA	\$ 24,258	\$ 24,762	\$ (504)
10	LILLY	\$ 23,045	\$ 21,583	\$ 1,462
11	AMGEN	\$ 18,621	\$ 17,103	\$ 1,518
12	ABBVIE	\$ 18,150	\$ 17,881	\$ 269
13	BOEHRINGER INGELHEIM	\$ 17,375	\$ 16,889	\$ 486
14	BAYER	\$ 17,276	\$ 16,431	\$ 845
15	NOVO NORDISK	\$ 14,300	\$ 12,576	\$ 1,724
16	TAKEDA	\$ 13,399	\$ 15,909	\$ (2,510)
17	ACTAVIS	\$ 12,742	\$ 12,375	\$ 367
18	MYLAN	\$ 11,087	\$ 10,325	\$ 762
19	BRISTOL-MYERS SQB.	\$ 11,023	\$ 12,756	\$ (1,733)
20	GILEAD SCIENCES	\$ 11,011	\$ 9,540	\$ 1,471
		\$ 491,455	\$ 490,895	\$ 560

Note: US\$: Sales and Rank are in US\$ with quarterly exchange rates

Sales cover direct and indirect pharmaceutical channel wholesaler and manufacturers

The figures above include prescription and certain over the counter data and represent manufacturer prices

Source: IMS Health MIDAS, December 2013

Retrieved: April 14, 2014

Some of the above losses can be explained by the loss of exclusivity of patented blockbuster drugs (sales revenue greater than US \$1 billion/year). From a 2014 article by EP Vantage, major revenue losses reported for patent blockbuster drugs occurred in 2011, 2012, and 2013. In addition, the reported losses were offset by new sales for the same years (Plieth & Fagg, 2014). (see Table 6)

Table 6 Global sales at risk of patent expiry (US\$Bn)

	2011	2012	2013	2014e	2015e	2016e	2017e	2018e
Total sales at risk	\$ 32.60	\$ 54.70	\$ 34.30	\$ 38.70	\$ 47.50	\$ 38.80	\$ 32.60	\$ 35.80
Actual sales lost or forecast to be lost	\$ (17.00)	\$ (38.20)	\$ (29.10)	\$ (24.00)	\$ (17.00)	\$ (15.60)	\$ (17.40)	\$ (15.60)
Sale replaced	\$ 36.00	\$ 47.00	\$ 26.80	\$ 54.20	\$ 58.40	\$ 60.40	\$ 62.90	\$ 58.60
Net of Sale replaced - Actual Forecast Sales Lost	\$ 19.00	\$ 8.80	\$ (2.30)	\$ 30.20	\$ 41.40	\$ 44.80	\$ 45.50	\$ 43.00

Note: Shaded area is projected

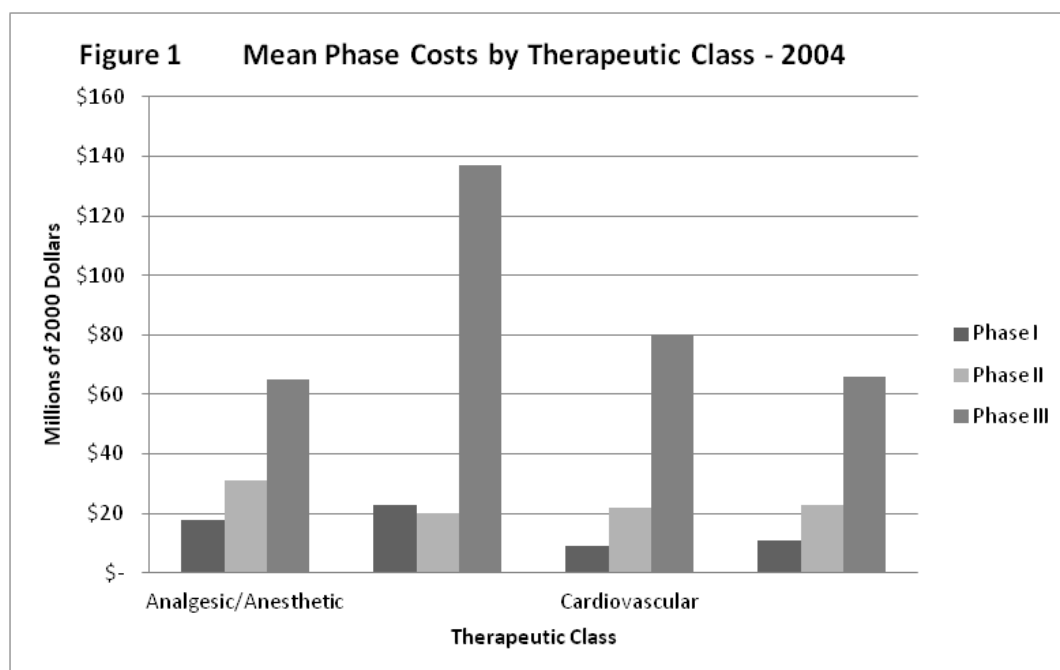
Source: <http://www.epvantage.com/Universal/View.aspx?type=Story&id=489880>

Retrieved: 3/18/2014

The projected total patent blockbuster drug losses for the years of 2014, 2015, 2016, 2017, and 2018 are offset by the projected sales increases for the same time period. Looking at the figures of projected losses and gains for 2014 to 2018, it appears the blockbuster drug productivity problem of the 1990s and early 21st century has abated. (see Table 6)

2.2 Pharmaceutical Industry Cost Structure

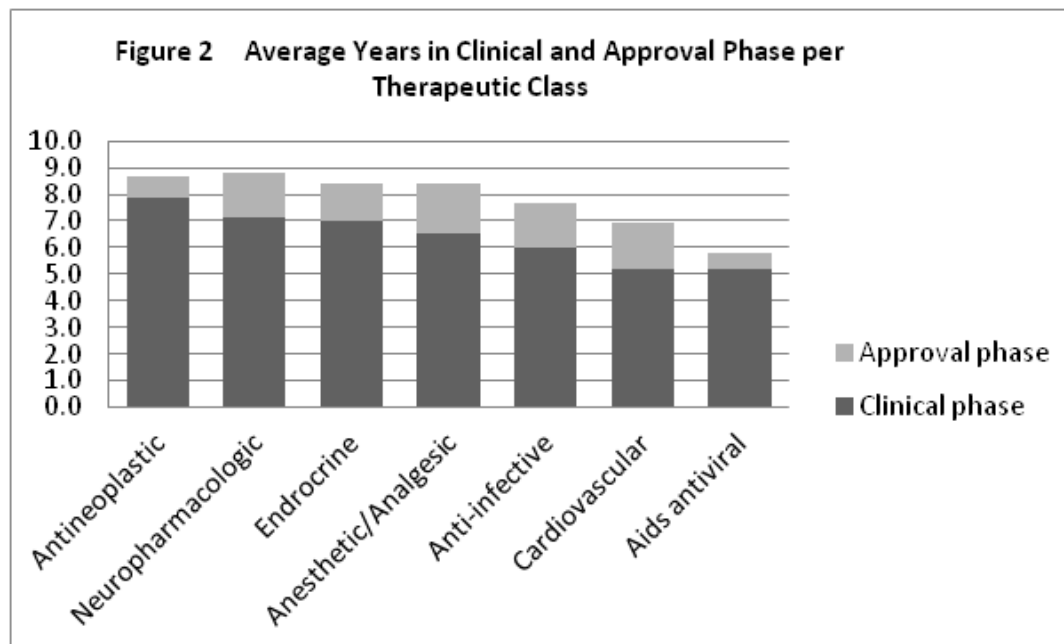
The pharmaceutical cost structure is very complicated. For example, some of the variations in the cost structure are dependent upon the phase of the drug pipeline and a drug's therapeutic class. The following figure displays how each therapeutic class has its own cost structure per clinical phase (DiMasi, Grabowski, & Vernon, 2004). (see Figure 1)



Source: R&D Costs and Returns by Therapeutic Category
Retrieved: April 11, 2014

Another example of different cost structure is in clinical development which on average takes about 7.2 years. However, clinical development is 5.2 years for AIDS antiviral drugs and 7.9 years for antineoplastic drugs, while neuropharmacologic and cancer drugs take about 9 years to transverse clinical trials (Kaitin, 2010). The longer the period of time that a drug spends in the clinical trials and approval phase, the higher the cost for drug development. (see Figure 2)

In addition, research, development, and license costs can be from 20% to 40% of the overall cost structure (Gassmann, Reepmeyer, & Maximilian “von” Zedtwitz, 2004). The other costs in developing a drug are production (15-30%), technical and administration (5%-15%), marketing and distribution (20%-30%), and profit margin (20%-35%) (Gassmann et al., 2004).

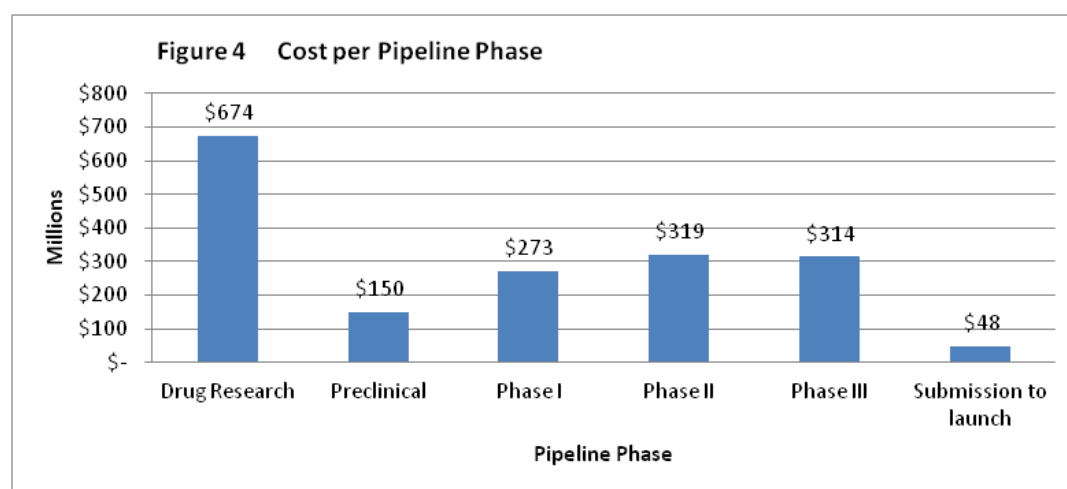
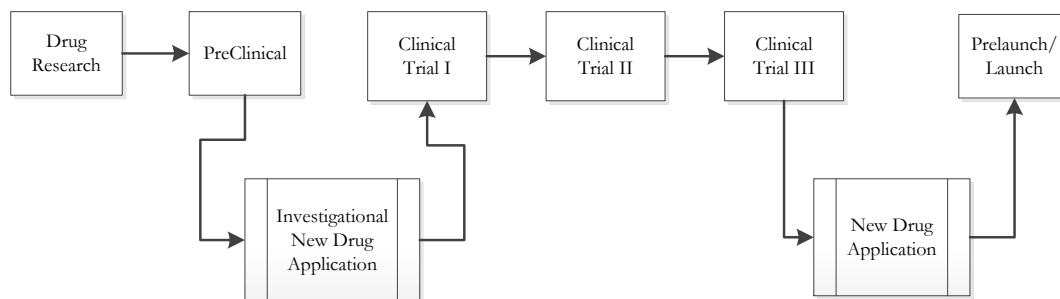


Source: Deconstructing the Drug Development Process: The New Face of Innovation
Retrieved: June 25, 2014

2.3 Pharmaceutical R&D Structure, Process, and Cost

2.3.1 R&D Structure

You must understand the structure and the process of pharmaceutical industry research and development (R&D) to see the effects it has on the costs and productivity. Cost and productivity affects profits. First we start with an analysis of the drug discovery and development process structure, which is referred to as the drug pipeline (Long & Works, 2013). (see Figure 3) If we take a quick look at the possible cost per stage of the pipeline, we will begin to see the complexity in the drug design and development (Paul et al., 2010). (see Figure 4)

Figure 3 Pharmaceutical Drug Pipeline

Source: How to improve R&D productivity: the pharmaceutical industry's grand challenge
Retrieved: March 27, 2014

2.3.2 R&D Process

It may take 10-15 years before a drug is released to the market from the drug pipeline (Clinuity, 2009; Danzon, Nicholson, & Pereira, 2005; Long & Works, 2013; Paul et al., 2010). The drug pipeline is broken up into multiple development phases: drug research, preclinical, clinical trial phase I, clinical trial phase II, clinical trial phase III, pre-launched, launched, phase IV, and suspended (Lloyd, 2014; PhRMA, 2014). The drug research phase is broken into multiple parts which we will not discuss in detail in this paper. The drug research phase

begins with five to ten thousand compounds which are reduced to about 250 compounds that will enter the preclinical phase. (Clinuity, 2009)

Preclinical testing is where the lead compound is involved in laboratory and animal testing to indicate whether the compound is suitable for human testing (Long & Works, 2013; PhRMA, Unknown; Sobel & Reisner, 2008). Researchers determine the efficacy levels, side effects, absorption, distribution, metabolism, elimination and duration of the lead compound. Included in the preclinical phase are methods that are developed to make large quantities of the lead compound which are of commercially viable purity (Sobel & Reisner, 2008). Before the lead compound can enter clinical testing, the research company needs to file an Investigational New Drug (IND) Application with the FDA. The FDA review of the IND takes about 30 days (Sobel & Reisner, 2008).

The time it takes from the start of the drug research phase to the end of preclinical phase is about three to six years (Paul et al., 2010). About five drugs are submitted from the end of the preclinical phase for an IND and, if accepted, will progress to the first clinical phase using human patients (Long & Works, 2013; Paul et al., 2010). During the preclinical phase, active compounds can be formulated into different forms which can be patented. (Sobel & Reisner, 2008) Thus, pharmaceutical and biotechnology patents are applied to formulations, compounds, nucleic acids, proteins, antibodies, research tools, methods of manufacture, and methods of treatment (Sobel & Reisner, 2008).

After the drug research and preclinical phases, clinical trials are next where a prospective compound is tested on human volunteers. The clinical trials consist of phase I, phase II, and phase III. It takes about two to ten years, with an average of five years, for a drug to successfully pass all three phases in clinical trials (The Campbell Family Cancer Research Institute, Unknown). All phases of the clinical trials are conducted by the

pharmaceutical company who submitted the drug for clinical trials or its designee (NIH, 2012). These clinical trials are highly regulated by governments according to good clinical practices (GCP) which include adequate human protection (HSP) (FDA, 2014a). In some countries, GCP have been adopted as laws and/or regulation (College, 2014). The FDA regulations concerning clinical trials include both GCP and HSP which have been in effect since the 1970s (FDA, 2014a; Vijayanathan & Nawawi, 2008).

After the IND is accepted by the FDA, the prospective drug begins phase I of the clinical trials (PhRMA, 2014). The purpose of phase I of the clinical trial is to test for safety, tolerability, and chemical structure effects on the body (The Campbell Family Cancer Research Institute, Unknown). There are usually a hundred or fewer healthy volunteers for phase I trials (PhRMA, Unknown). After the drug has successfully completed the phase I trial, the phase II trial will begin using about 100 to 500 volunteers that have the disease or condition that the drug is supposed to treat (PhRMA, Unknown). The purpose of this trial is to test the drug efficacy and dose response (PhRMA, Unknown; The Campbell Family Cancer Research Institute, Unknown). By the end of the first two trials the drug has been tested against humans for safety and efficacy (Sobel & Reisner, 2008; The Campbell Family Cancer Research Institute, Unknown). The phase III trial is a randomized test against a placebo using 1,000 to 5,000 patients throughout the world. The phase III trial may take multiple years and millions of dollars in an attempt to show the drug is statistically effective against the condition or disease it is supposed to treat (FDA, 2013c). The results of the phase III trial determine whether the drug is released to the market.

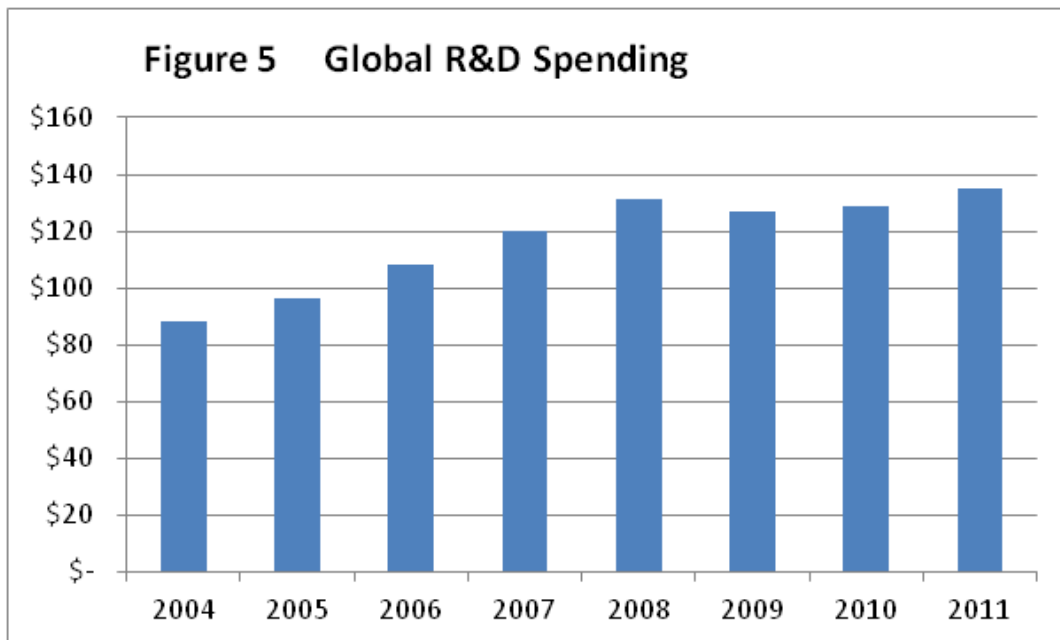
After the clinical trials are successful, the data from the preclinical and the three clinical trials are collected for as part of the New Drug Application (NDA) to the Center for Drug Evaluation and Research (CDER) which is part of the FDA (FDA, 2013d). Upon

receipt of the NDA, the FDA has 60 days to review and to approve or not approve the NDA (FDA, 2014c). As part of the NDA, a fee is paid to CDER by the submitting pharmaceutical company according to the Prescription Drug User Fee Act (PDUFA). Because of the PDUFA, FDA (CDER) will take six months to two years to approve the application (DiMasi, Hansen, & Grabowski, 2003; FDA, 2014d). Once the application is approved by CDER, the drug can be marketed according to its label.

Post-approval research and monitoring, also called phase IV clinical trial, is conducted after the release of the drug to the market. The purpose of the phase IV clinical trial is to continue to monitor the long term effects of the drug in terms of safety and efficacy and may be required as a condition to its release to the market.

2.3.3 R&D Costs

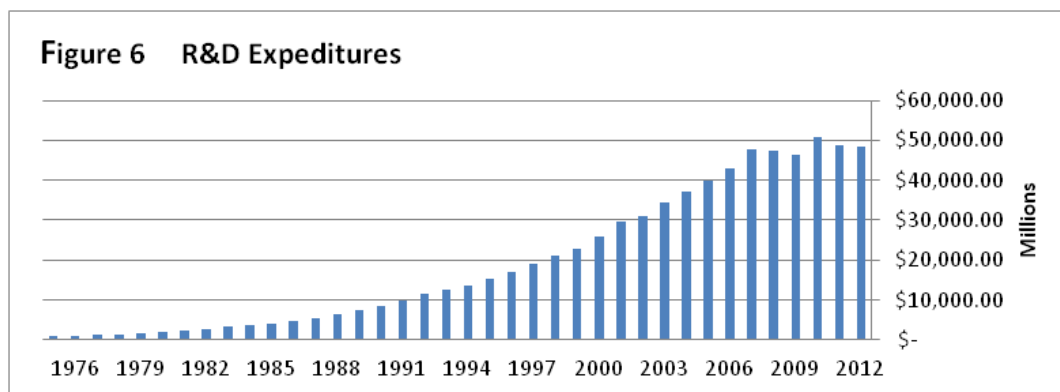
According to 2011 PhRMA members' data, about 15.9% of the global pharmaceutical industry revenues go toward research and development (R&D) expenditure (PhRMA, 2013). The EvaluatePharma report of 2012 has an 18.8% ratio of global R&D to global revenues in 2011, and as global pharmaceutical sales increased, global R&D spending increased from 2004 through 2011 (EvaluatePharma, 2014). (see Figure 5)



Source: EvaluatePharma World Preview 2018: Embracing the Patent Cliff

Retrieved: June 12, 2014

Again, using data from 2011 PhRMA members' data, R&D expenditure steadily increased until 2007 when it flattened out (PhRMA, 2013). PhRMA members' R&D cost reached a peak in 2010 at \$50.710 billion and by 2012 the cost had dropped to \$48.485 billion (PhRMA, 2013). (see Figure 6)



Source: PhRMA Annual Membership Survey July 2013

Retrieved: March 12, 2014

There are many reasons that would explain the increased R&D spending. One reason is due to technological advances that allow the pharmaceutical industry to identify

many more targets to develop New Molecular Entities (NMEs) for cures or therapy (Cockburn, 2004; Ruffolo, 2006). However, there is an ambiguity on the known number of drug targets (Overington, Al-Lazikani, & Hopkins, 2006). A literary review on drug targets found an article dated 1997 by Drews and Ryser, that estimated there are 483 drug targets (Overington et al., 2006), but in 2000 Jurgen Drews estimated that the number of drug targets are from 5,000 to 10,000 due to the human genome that contains about 300,000 genes (Drews, 2000). The human genome was sequenced in 2002 which gave way to estimates of about 8,000 possible drug targets, where about 5,000 targets might be targets of traditional drug compounds of antibodies (~2,400 targets) and by protein drugs (~800 targets) (Imming, Sinning, & Meyer, 2006). From the studies of ligand-binding, the number of targets identified are 399 molecular targets from 130 protein families and another approximately 3,000 targets for small molecule drugs from prediction of the human genome (Imming et al., 2006). Tams Bartfai and Graham V. Lees state that there were roughly 250 targets in 2001, which increased to 600 by 2005 (Bartfai & Lees, 2010). In 2006, there are two papers, one by Imming et al. and another by Overington et al. that gave an estimate of 218 and 324 drug targets respectively (Imming et al., 2006; Overington et al., 2006). In 2007, David S. Wishart et al. reported the number of non-redundant drug targets to be 3,027 in the 2.0 DrugBank (Wishart et al., 2008). In conclusion, the number of drug targets is unknown.

Another reason for the increase in R&D spending is the retooling with new technologies and research capabilities (Cockburn, 2004). In addition, the diseases which are the drug targets are becoming more complex, harder to understand, and difficult to attack (Cockburn, 2004). In addition, long-term drug toxicity to humans requires longer trials and adds to the development costs of the drug (Kaitin, 2010). Government regulations have also added cost to drug development costs. For example, the 1962 Kefauver Harris Amendment

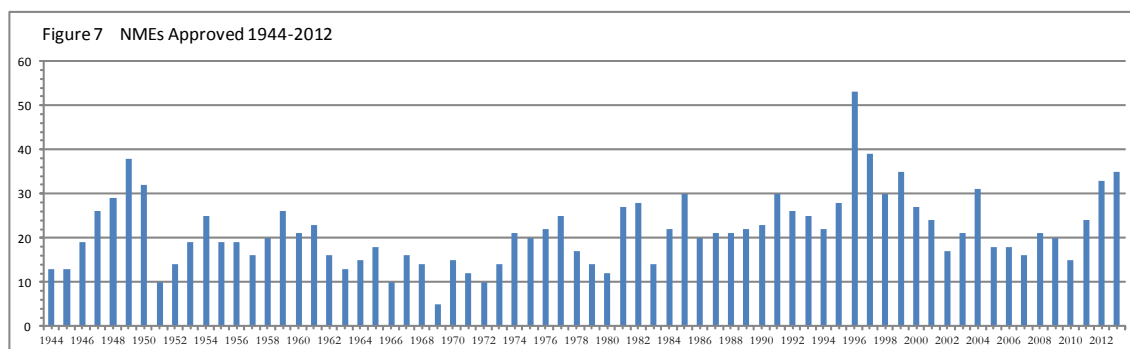
to the FD&C Act requires that a drug has to be safe but it has to demonstrate efficacy against a placebo (Scannell, Blanckley, Boldon, & Warrington, 2012). Other reasons that drug development costs rise are failure in the late-phase clinical trials (Pammolli, Magazzini, & Riccaboni, 2011), a focus on new therapeutic targets (Pammolli et al., 2011), and the drug research phase has become research intensive because the drug interaction is at the molecular level (Cockburn, 2004; Pammolli et al., 2011).

2.4 R&D Drug Productivity Costs

The R&D cost per NME reported by the IFPMA was over \$1.3 billion for 2012 (International Federation of Pharmaceutical Manufacturer & Associations, 2012), and the Analysis Group reported in 2013 that the development cost per NME was \$1.2 billion in 2005 dollars value (Long & Works, 2013). A published report in 2010 by Steve Morgan et al. concluded that in spite of thirty years of research into the cost of NME, no one has reported a cost estimate that can be considered to be a gold standard (Morgan, Grootendorst, Lexchin, Cunningham, & Greyson, 2011). Thus, I will provide an estimate for the cost per NME. As a further note, biologicals are not included in this analysis due to inconsistent reporting of biologicals approved each year until 2004, when the FDA included biologicals in their report.

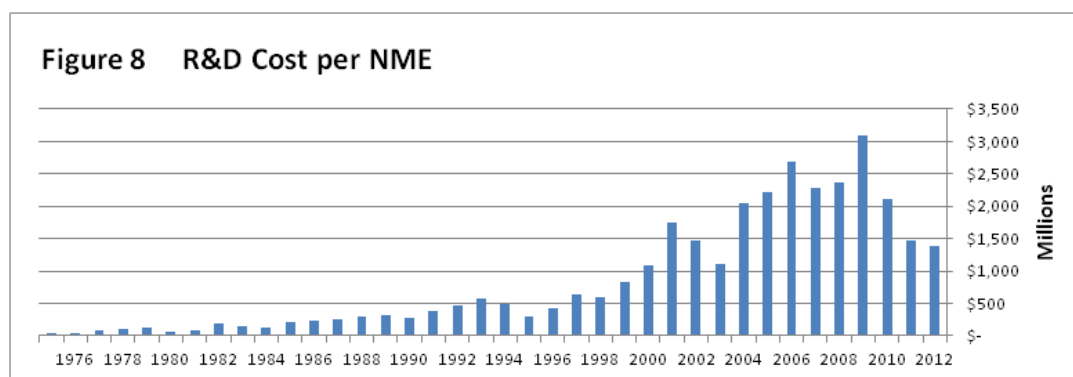
By examining the FDA data on the number of NMEs approved per year from 1944 to 2012, the pharmaceutical industry reached a peak in 1996 with 53 NMEs approved by the FDA (FDA, 2013e). Further analysis of the data and graph of the NMEs approved by the FDA from 1944 to 2013 provides several pieces of information. (see Figure 7) My calculations show the average number of NMEs from 1944 to 2013 to be 21 NME per year. In addition, there are several cycles in the graph, starting with 1944 to 1950 where there was a steep increase in NMEs and then the number dropped in 1951. Two more cycles occurred

from 1951 until 1969 and from 1969 until 1980. A large cycle occurred from 1980 until 2009 and included the 1996 peak of 53 NMEs. From 2010 to 2013, there was a rise in the number of NMEs.



Source: FDA: Summary of NDA Approvals & Receipts, 1938 to the present
Retrieved: March 13, 2014

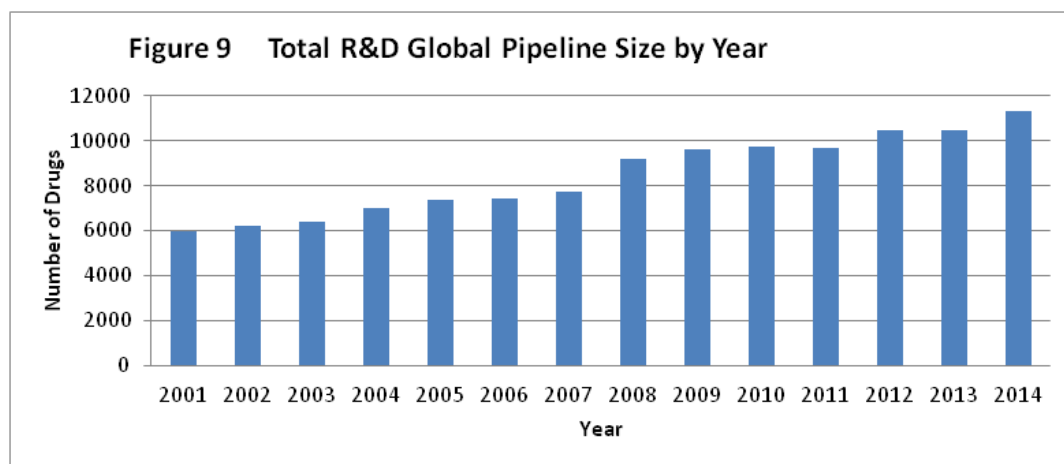
Using PhRMA member's data for 2013 and the FDA NME data, we examine the United States R&D expenditure per NME approved by the FDA for a year. Thus, we provide a rough estimate of R&D cost per NME per year in the United States. The analysis of these calculations indicates that the R&D cost per NME broke the \$1 billion mark in 2000 and continued on an upward trend until 2009, when the cost per NME started to have a downward trend to 2012. The highest cost to develop an NME was in 2009 at a cost of \$3.096 billion per NME. (see Figure 8)



Source: FDA: Summary of NDA Approvals & Receipts, 1938 to the present and PhRMA Annual Membership Survey July 2013
Retrieved: March 12, 2014

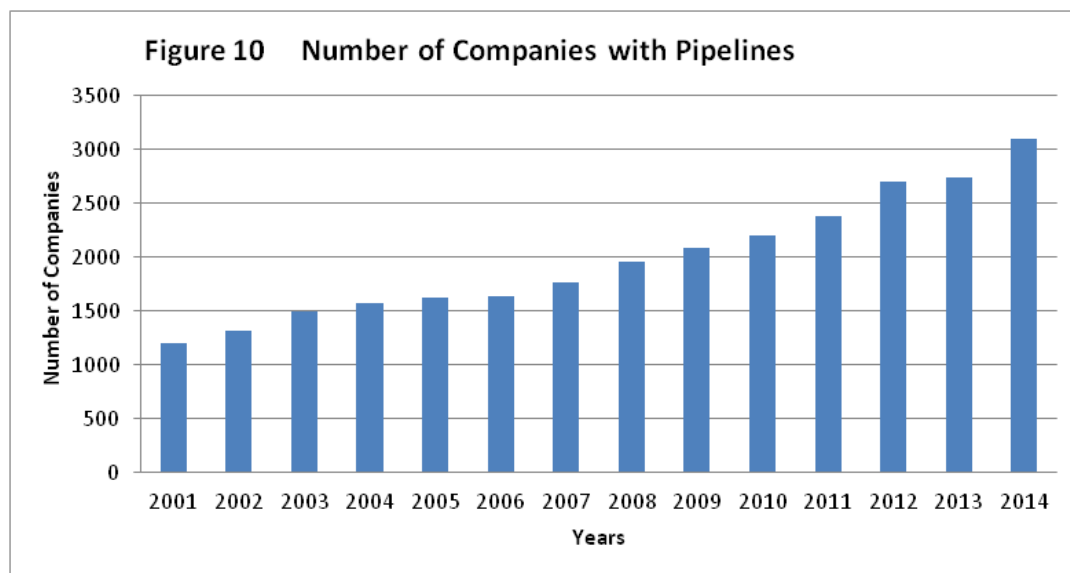
Pharmaceutical industry productivity or innovation is measured by the number of NMEs and biologicals approved by CDER per year and the cost of R&D per year. Many papers have stated that pharmaceutical industry productivity is decreasing due to multiple reasons such as mergers (Danzon & Nicholson, 2012; Demirbag, Ng, & Tatoglu, 2007; LaMattina, 2011), absence of easy identifiable drugs (Scannell et al., 2012), and high failure rates in phase I, II, and III trails (Pammolli et al., 2011). The cost of drug development is increasing at a rate that only the large pharmaceutical companies can afford it and may be a reason for pharmaceutical mergers and acquisitions or alliances (Danzon & Nicholson, 2012; Gassmann et al., 2004). Some estimates of the drug success ratio from clinical trials to market is one out of five and from the entire drug pipeline to market the estimated ratio is from one out of twenty-four (Paul et al., 2010) to one out of 10,000.

Next we analyze the current data that is available to see if these accusations are true. We start with the 2014 Citeline Pharma R&D Annual Review report (Lloyd, 2014). The Citeline Pharma R&D report provides a graph that indicates the global pharmaceutical industry pipeline has been increasing since 2001 (5995 drugs) to 2014 (11307 drugs); the pipeline is 1.89 times larger in 2014 as compared to 2001 (Lloyd, 2014). (see Figure 9)



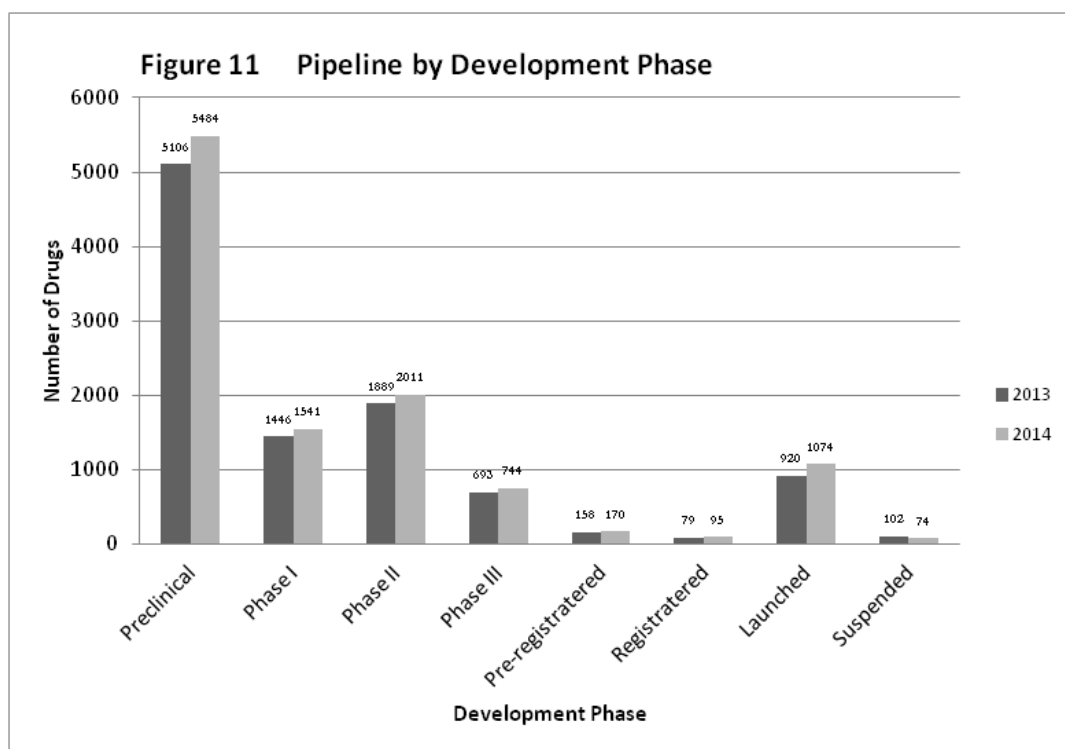
Source: Citeline Pharma R&D Annual Review 2014
Retrieved: March 23, 2014

Addition data from this report indicates that the number of companies that have active pipelines has increased from 2001 (1198) to 2014 (3107) for an overall increase of 260% (Lloyd, 2014). (see Figure 10)



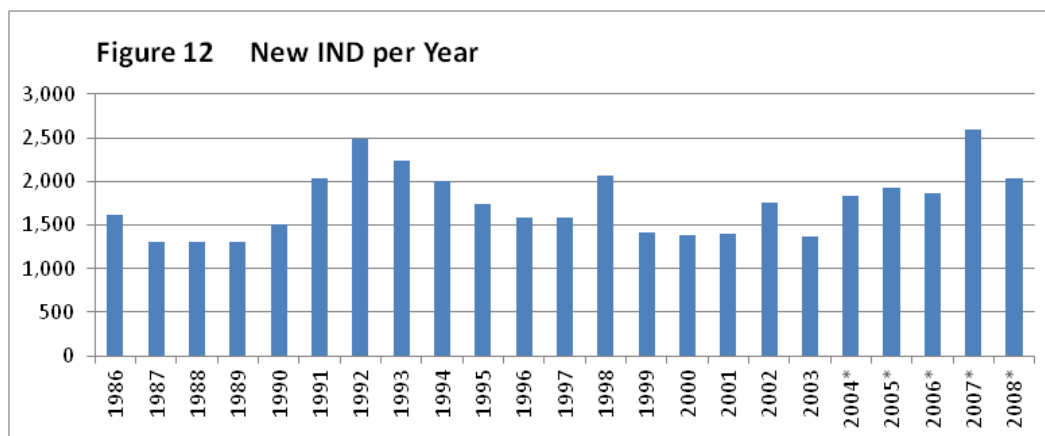
Source: Citeline Pharma R&D Annual Review 2014
Retrieved: March 23, 2014

The Citeline report further stated that the drug pipeline from 2013 to 2014 had increased in all phases (Lloyd, 2014). (see Figure 11)



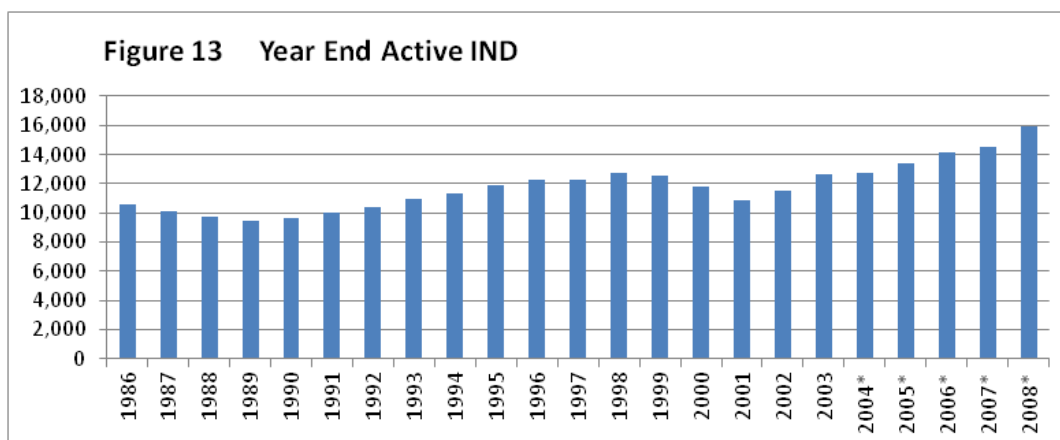
Source: Citeline Pharma R&D Annual Review 2014
Retrieved: March 23, 2014

A review of the Investigational New Drug (INDs) applications received from 1986 to 2008 data and graph (see Figure 12) provides the following information (FDA, Unknownb). The number of INDs received from 1987 to 1989 was flat and afterwards reached a peak in 1992. After 1992, the number of INDs received decreased until 1999 and then remained roughly flat until 2003. After 2003, the number of INDs received increased from 2004 to 2008 (FDA, Unknownb).



Note: * 2004 to 2008 included biologics
 Source: FDA: CDER ORIGINAL INDs RECEIVED CALENDAR YEARS 1986 - 2008
 Retrieved: March 28, 2014

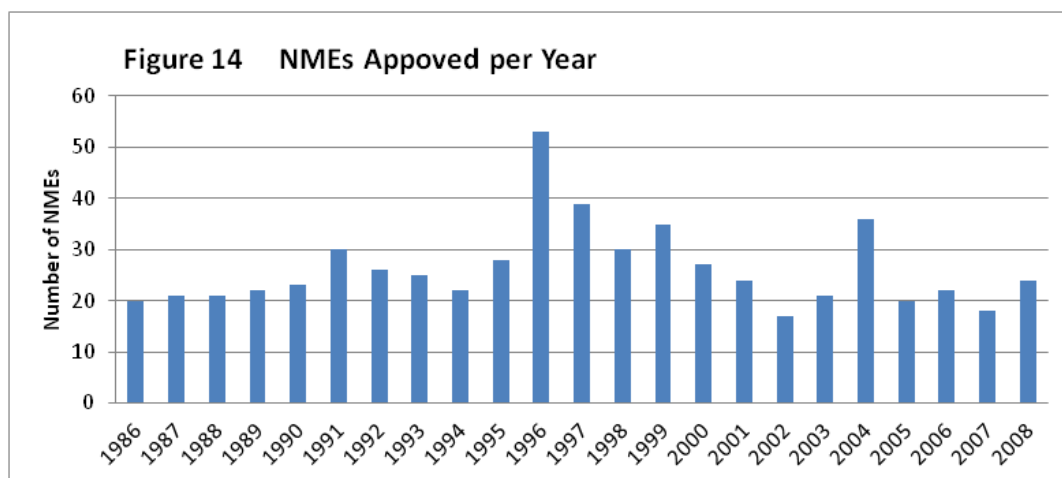
A review of the Number of Active INDs in phase I, II, and III at the close of the Calendar Year data and graph (see Figure 13) provides the following information (FDA, Unknown). The number of INDs active in the clinical phases decreased from 1986 to 1989. Afterwards, the number of active INDs in the clinical phases increased until 1998, then decreased during the years of 1999 and 2000. The number of INDs active in the clinical phases increased from 2001 to 2008, where the data ends.



Note: * 2004 to 2008 included biologics
 Source: FDA: CDER NUMBER OF ACTIVE INDs AT THE CLOSE OF THE CALENDAR YEARS 1986 - 2008
 Retrieved: March 28, 2014

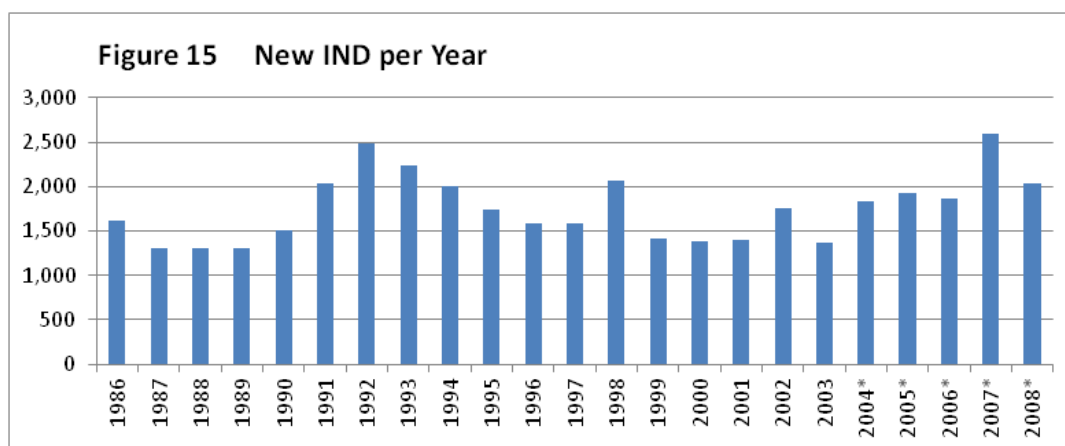
Generally, the period from 1980 to the 1996 indicates the number of NMEs approved was increasing and then afterwards decreased until 2009. Upon further review, the

number of NMEs approved increased from 1980 until 1991 and then decreased after 1991 until 1994. The period of interest is the time period from 1995 until 2000 when the number of NME approved hit its peak and then continued in a downward trend until 2009. This is referred to as the pharmaceutical industry productivity decline because the number of NMEs was declining and yet the cost of R&D was going up (FDA, Unknownb). (see Figures 7 and 14)



Source: FDA: Summary of NDA Approvals & Receipts, 1938 to the present
Retrieved: March 13, 2014

The productivity of the drug pipeline has a high correlation to the number of INDs submitted to clinical trials. Since it takes about four to five years for an IND to clear clinical trials and become a drug, I would expect to see a peak in IND submittal four to five years before the 1996 peak and we do see a peak in 1992. Furthermore, the number INDs increase from 1990 to 1992 and then decrease from 1993 to 2003. This correlates to the increase of drugs approved from 1995 to 1996 and then the decrease from 1997 to 2007. (see Figure 15)



Note: * 2004 to 2008 included biologics

Source: FDA: CDER ORIGINAL INDs RECEIVED CALENDAR YEARS 1986 - 2008

Retrieved: March 28, 2014

If you take the number of approved NMEs and divide them by the number of INDs received for the same year and then do an average of this figure for the years of 1986 to 2008, the average drug productivity per year would be about one to two NMEs approved per one hundred INDs submitted from 1986 to 2008, which is a much lower than the 1 out of 25 or 1 out of 5 others have quoted.

2.5 Counterfeit Medicine

2.5.1 Introduction

Because disease has plagued earth for millions of years (Capasso, 2005; McLain, 1991), medicine and their recipes have been in existence in an herbal, animal, or mineral form since early man to combat these diseases and other maladies (Ji, Li, & Zhang, 2009; Venzmer & Koenig, 1972). There is a high probability that someone has modified someone else's medical recipe and used it during this period. Today's equivalent would be cook books where old recipes have been given a new slant with new or different ingredients. Since none of the cook books would be regarded as the official standard cook book, the changed recipes would not be considered to be counterfeit recipes.

A Greek physician Pedanius Dioscorides in the 1st century C.E. created a formal document called *Materia Medica* that was accepted as a standard (Ji et al., 2009; Parker, 1915). The *Materia Medica* contain about 600 plants and 1000 drugs recipes (DerMarderosian, 1996) and could be called the first pharmacopeia (De Vos, 2010). *Materia Medica* was considered the official medical text until the beginning of the 19th century (De Vos, 2010).

Since the creation of the *Materia Medica*, several civilizations have added to this medical text. It was the responsibility of physicians to make medicine for their patients from the *Materia Medica* and add to the *Materia Medica*. It wasn't until the Islamic empire around 8th century or 9th century C.E that apothecary shops were created (Al-Ghazal, 2003; Hamarneh, 1962; Syed, 2002) and inspected by a syndic (Muhtasib) in Baghdad and elsewhere for the sole purpose to eliminate counterfeit medical recipes (Syed, 2002). It was the responsibility of the apothecary to make the medicine for the physician or for a patient from a prescription from a physician. Since then, there have been many incidences of counterfeit medicine and nostrums given or prescribed to a patient. It was not until the late 19th century that western governments started to seek control over medicine for the purpose of safety, efficacy, effectiveness, and correct formulary.

One item of note that is often left out of the many reports on counterfeit drugs is that the cost of pharmaceutical-branded prescription drugs is in the drug's development and not in its manufacturing (Davison, 2011). This is one of the many reasons the selling of counterfeit drugs is so lucrative. A branded prescription drug is usually patented, which allows the drug developer to charge a high price to reimburse the cost of the development of the prescription drug and other drugs whose development has failed.

2.5.2 Definition of Counterfeit Medicine

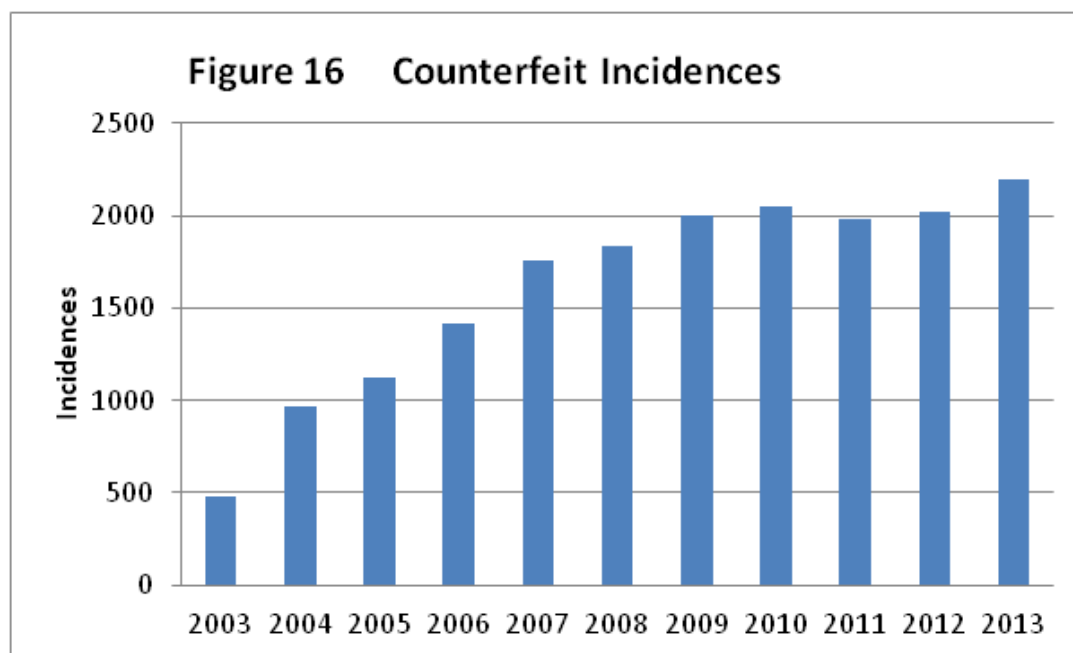
One of the problems with the term "counterfeit medicine" is its definition as many nations and organizations cannot seem to agree on a single one (Chika, Bello, Jimoh, & Umar, 2011; Wertheimer & Wang, 2012). Counterfeit medicine in one nation may not be a counterfeit medicine in another. For example, India, which is the number one exporter of counterfeit drugs, never uses the word "counterfeit" but uses the term "spurious drugs" instead (Gautam, Utreja, & Singal, 2009). The World Health Organization (WHO) has their own definition (World Health Organization, 2007); the Pharmaceutical Security Institute definition is based upon the WHO definition (Pharmaceutical Security Institute, 2014d). The US Federal Food, Drug, and Cosmetic Act also defines a counterfeit drug differently than the WHO (World Health Organization, 2007). We will define a counterfeit drug or medicine for this thesis to be a drug that is deliberately and fraudulently mislabeled with respect to identity and/or source, tampered with, adulterated, spurious in nature, and/or just generally substandard. This definition applies to brand and generic drugs which include gray pharmaceuticals.

The gray pharmaceutical market consists of unregulated secondary wholesalers that sell drugs of unknown source, quality, and efficacy. Sometimes these drugs are stolen and are sold at a discount price. Other times, these gray market drugs are counterfeit. The gray pharmaceutical market also is referred to as parallel drug trade (Finlay & Center, 2011).

2.5.3 Cost of Counterfeit Medicines

What is the cost of counterfeiting drugs and how prevalent is drug counterfeiting? WHO estimates that 10% of worldwide medicine is counterfeit (UNICRI, 2012). Nations that have an effective law enforcement and pharmaceutical supply chain (PSC) control experience about 1% or less of their market price in counterfeit medicine (Fernandez,

Green, & Newton, 2008; World Health Organization, 2008). Whereas in some countries the percentage of counterfeit medicine can be as high as 30%, which includes several countries in Africa and parts of Asia and Latin America (Attaran, Bate, & Kendall, 2011; Fernandez et al., 2008; World Health Organization, 2008). In 2013, the Pharmaceutical Security Institute (PSI) reported 2,193 incidents of pharmaceutical crime that involved 317 different pharmaceutical products in 124 nations (Pharmaceutical Security Institute, 2014a; Pharmaceutical Security Institute, 2014b; Pharmaceutical Security Institute, 2014c). (see Figure 16) WHO estimated in 2003 that the counterfeit medicine was worth \$32 billion (Chika et al., 2011) and with a expansion rate of 13% per year that became a \$75 billion global business by 2010 (Attaran et al., 2011; Chika et al., 2011; Pitts, 2009; World Health Organization, 2007). My own calculation is that the counterfeit medicine was a \$109 billion business by 2013. With the GAO reporting that there were over 34,000 rogue Internet pharmacies (United States Government Accountability Office, 2013) and with LegitScript only verifying 214 online pharmacies to be legitimate (LegitScript LLC, 2013), the percentage of rogue pharmacies on the Internet is greater than 99%.



Source: Pharmaceutical Security Institute: Incidents Trends

Retrieved: April 4, 2014

Since 2010, the U.S. Immigration and Customs Enforcement (ICE) Homeland Security Investigations (HSI) has participated in an operation called Apothecary. The purpose of Operation Apothecary is to combat the use of the Internet for illegal drug distributions and has so far resulted in 1,048 seizures that had MSRP value of \$20 million, 115 arrests, and 112 indictments which resulted in 99 convictions (U.S. Department of Homeland Security, 2014).

In 2013, ICE reported to Congress that a worldwide collaboration of 100 nations was involved in an operation called Pangea VI. The purpose of this operation was the targeting of illicit websites for selling counterfeit medicine. The result of the operation was a seizure of 10 million units (tablets or capsules) of counterfeit medicines worth about \$36 million and 13,763 illicit online pharmacy web sites were shutdown (INTERPOL, 2014a; U.S. Department of Homeland Security, 2014).

From 13 to 20 of May 2014, 111 countries and 196 agencies participated in Pangea VII. Pangea VII resulted in 9.4 million units of fake or counterfeit drugs seized that had a street value of \$36 million. In addition, Pangea VII resulted in 239 arrests and more than 10,600 websites shutdown (INTERPOL, 2014a).

2.5.3.1 Human Cost

In the U.S., the Internet is problematic for controlling counterfeit drugs. Nearly one out of four adults surveyed had purchased drugs online. As reported in a United States Government Accountability Office (GAO) report that was dated 2013, thirty-percent of those who purchased drugs online didn't understand how to buy drugs safely online (United States Government Accountability Office, 2013). In addition, the same GAO report stated that many of the online pharmacies were fraudulent businesses. These fraudulent online pharmacies are commonly known as "rogue" websites. Although the total number of rogue Internet pharmacies is unknown, the GAO reported that there were over 34,000 active rogue Internet pharmacies as of April 2013 (United States Government Accountability Office, 2013).

LegitScript is a privately owned company founded in 2007 whose functions are to actively track online pharmacies and dangerous health products, provide threat assessments of public and brand integrity, provide online reports about online pharmacies and health product, evaluate drugs and health products for safety, and provides certification for online pharmacies that is recognized by the National Association of Boards of Pharmacy (NABP).

As of June 2014, LegitScript has found 37,900 active Internet pharmacies, of which 35,839 are not legitimate. LegitScript has verified 214 online Internet pharmacies to be legitimate. This would indicate that more than 94.6% of the online pharmacy websites are illegitimate (LegitScript LLC, 2014). Besides the fact that these rogue Internet pharmacy

websites are fraudulent, they are also in violation of several state and federal laws by selling unapproved, counterfeit, or out-of-date drugs and controlled substances to locations in the United States.

One example of buying counterfeit drugs online occurred in 2010 during the H1N1 flu scare when generic Tamiflu was being sold on the Internet (Green, Nettey, & Wirtz, 2008; Mackey & Liang, 2011). Authorities purchased generic Tamiflu without a prescription from a legitimate looking website which was an illegal online pharmacy. An examination of the drug obtained had found no API. The drug contained an antibiotic similar to penicillin which would have been harmful or life-threatening to anyone allergic to penicillin (FDA, 2013f).

Another example occurred in 2008 in Singapore. In the first five months of the year, 150 people who reported being sick were found to have severe hypoglycemia, a sudden decrease of blood sugar levels. Four out of the 150 people died and seven suffered severe brain damage (Kao et al., 2009; World Health Organization, 2010). This was caused by a counterfeit erectile dysfunction drug that contained large doses of glyburide, which is used to treat diabetes (Kao et al., 2009).

As reported by a PLoS Medicine article dated 2008, an investigation into an anti-malaria drug was conducted by INTERPOL and Western Pacific World Organization Regional Office. The two agencies took samples of genuine and counterfeit artesunate from the nations of Vietnam (75), Cambodia (48), Lao PDR (115), Myanmar (Burma) (137), and at the Thai/Myanmar border (16) (Newton et al., 2008). The samples believed to be counterfeit (195/391) were found to contain no active product ingredient or too little to be effective. In addition, the report claimed there was a large amount of counterfeit artesunate drug on the market. The counterfeit artesunate drug has led to deaths from untreated malaria, reduced

confidence in the artesunate drug, and caused large economic losses for legitimate manufacturers. The PLoS Medicine report made a further claim that malaria might become drug resistant due to the artesunate drugs because of the low dosage of artesunate in the counterfeit drugs (Newton et al., 2008).

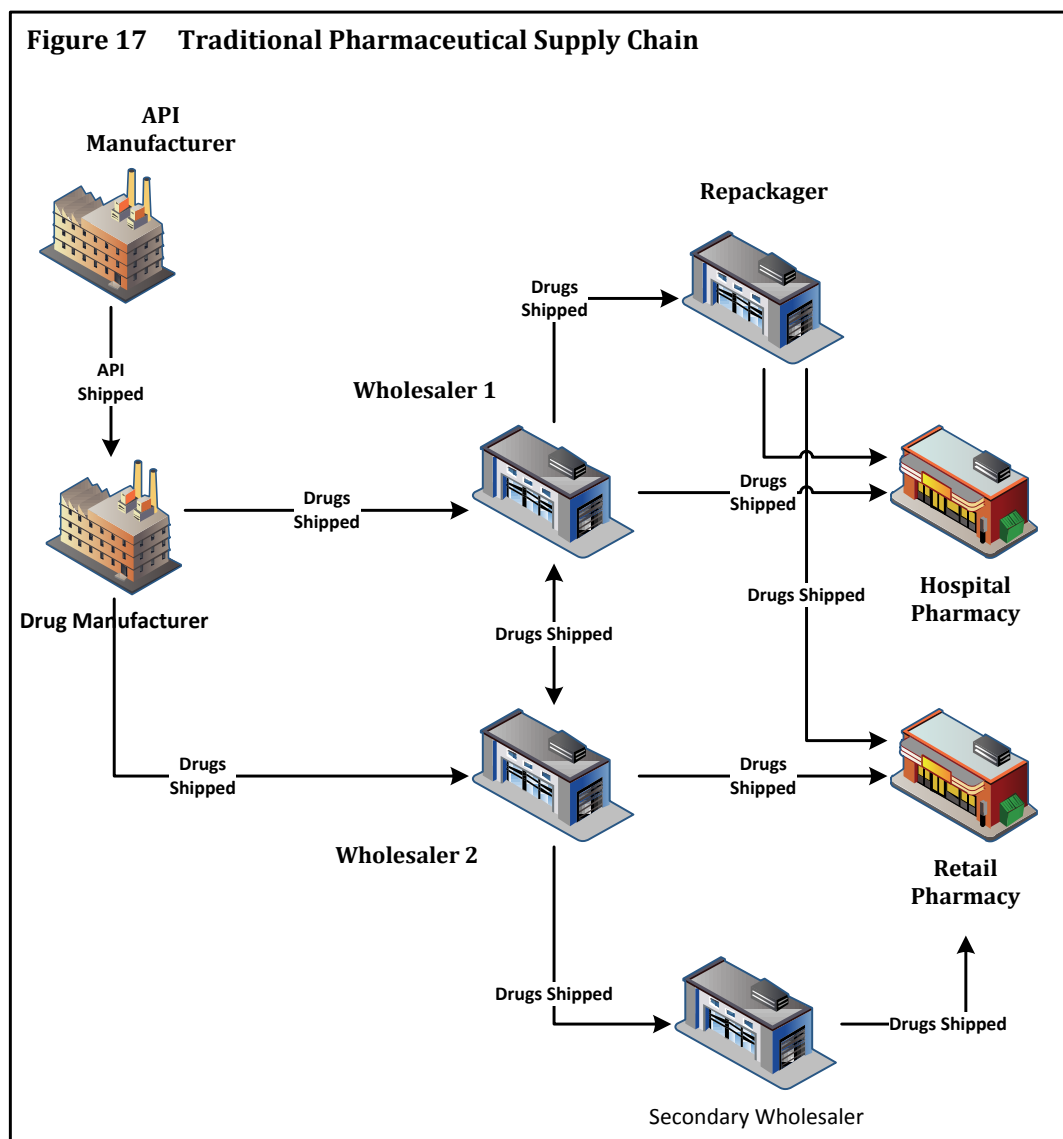
The worldwide death totals due to counterfeit drugs is unknown, as is the scale of the counterfeit business. What we do know is that there is a human cost, such as the several hundred people who died over a single incident of counterfeit drug due to its toxicity. Furthermore, you need to include the tens of thousands of people that did not die but may have been made very sick or prolonged their sickness from counterfeit (substandard) drugs. Counterfeit (substandard) drugs can create drug resistance infections, increase hospital stay, additional doses of the drug be required. In addition, new drugs will have to be developed to replace the ineffective drug, which will increase costs to the patient and health care system. Due to counterfeit drugs, the consumer may pay more for their drugs because pharmaceuticals companies have to pay for higher insurance rates, damage claims, and loss of revenues (JDS Uniphase Corporation, 2013).

To give some additional numbers to the human cost:

- Counterfeit tuberculosis and malaria drugs kills 700,000 people a year (Attaran et al., 2011; UNICRI, 2013);
- Counterfeit vaccine for meningitis caused 60,000 people in Nigeria to suffer with 2,500 to 3,000 killed in 1995 (J. Morris & Stevens, 2006; Paradise, 1999).

2.5.3.2 Corporate Cost

By looking at the PSC, we see the number of businesses that would lose revenues due to counterfeit drugs purchased online or from retail pharmacies. (see Figure 17)



There is a corporate cost in combating counterfeit medicine whether it's in the pill size, shape, color, packaging, and labeling. In addition, there is the cost of recall that the manufacturer is burdened with when the counterfeit drug is discovered. Counterfeit drugs also increase the cost of insurance for liability (Davison, 2011).

Once a brand drug is discovered as being counterfeit, brand erosion begins immediately, as was the case with Tylenol (Davison, 2011; JDS Uniphase Corporation, 2013; Kaplan, 1998). The Tylenol adulteration in 1982 killed seven people in the Chicago area and caused Johnson & Johnson (J&J) to recall 31 million bottles of Tylenol from the market at a

retail value of \$100 million (Kaplan, 1998). In addition, the J&J brand's longstanding reputation of trustworthiness fell as its common stock dropped in value by \$2.31 billion (Dowdell, Govindaraj, & Jain, 1992). Furthermore, J&J experienced brand erosion of Tylenol and saw its market share drop from 37% to 7%. However, Tylenol did recover its leading market position after the product package was redesigned and with a heavy price promotion (Kaplan, 1998).

Brand drug owners have never faced any litigation for damages due to counterfeit versions of their drug. Thus, the actions taken by the brand owner to identify the offending drug, to determine whether it is counterfeit or not, to inform the public about the counterfeit drug, and to remove the brand drug from the market are steps taken to preserve their own image and the brand's image. This was the case of the Tylenol adulterations

2.5.3.3 Government Costs

Counterfeit drugs can cause the loss of public support in the healthcare system and government (Davison, 2011; JDS Uniphase Corporation, 2013). In severe cases of counterfeit drugs, politicians and regulators are also blamed for their lack of supervision of the healthcare system (JDS Uniphase Corporation, 2013). Counterfeit drugs can also increase government healthcare costs through increased spending on nurses, doctors, hospital time, and proper drugs to cure the patient (Davison, 2011; JDS Uniphase Corporation, 2013) and destroy a government image which might impact its international trade (Davison, 2011). Because of counterfeit drugs, there is an increased burden on the family, friends, and patients due to the increase financial cost of co-pays, insurance rates, and taxes (Davison, 2011). With the increasing threat of counterfeit drugs, governments are seeing an increase in the cost of labor because of hiring more regulatory personnel to oversee the pharmaceutical drug supply chain in the nation and abroad (Davison, 2011; JDS Uniphase Corporation,

2013; Yankus, 2007). For example, the U.S. FDA has offices in China, India, Costa Rica, Mexico, Chile, and Jordan for the purpose of overseeing the food and drugs exported to the United States.

2.5.3.4 Organized Crime

The United Nations Convention against Transnational Organized Crime (UNTOC) (2000) defines organized crime as a structured group of three or more persons, existing for a period of time and acting in concert with the aim of committing one or more serious crimes of offences...in order to obtain, directly or indirectly, an economic or other material benefit (UNICRI , Organized Crime Strategies in the Production and Trade of Counterfeit Medicine, p. 24).

This definition includes the Chinese triads, Colombian cocaine traffickers, Mexican Mafia, Russian Mafia, Hezbollah, and al Qaeda, which are all involved in the making and selling of counterfeit drugs (Bate, 2008; Finlay & Center, 2011; Mackey & Liang, 2011; Partnership for Safe Medicines, 2014).

Counterfeit medicine is a high profit and low risk enterprise for organized crime.

High profits are obtained for the following reasons:

- The equipment that is used for illicit drugs can be used for counterfeit drugs (UNICRI, 2013).
- Trade routes have already been established with the illicit drugs, which means organized crime can use the same means of corruption, intimidation, and extortion practices and includes the same methods of concealment and document forgery (Davison, 2011; INTERPOL, 2014b; UNICRI, 2013).

- The same alliances used in the illicit drug trade are used in the counterfeit drug trade (UNICRI, 2013).
- High demand for the counterfeit drugs by those who can't afford the drugs in the current market and for those persons seeking a counterfeit version of the drugs (JDS Uniphase Corporation, 2013; UNICRI, 2013; Wertheimer & Wang, 2012).
- New or used tablet machines that are used to produce the legitimate drug can be easily bought and used to produce counterfeit drugs (UNICRI, 2013).
- Cost of production is low and the selling price is very high (Davison, 2011; UNICRI, 2013).
- Cost of the contaminant is very cheap as compared to the API (Bate, 2008; Davison, 2011).

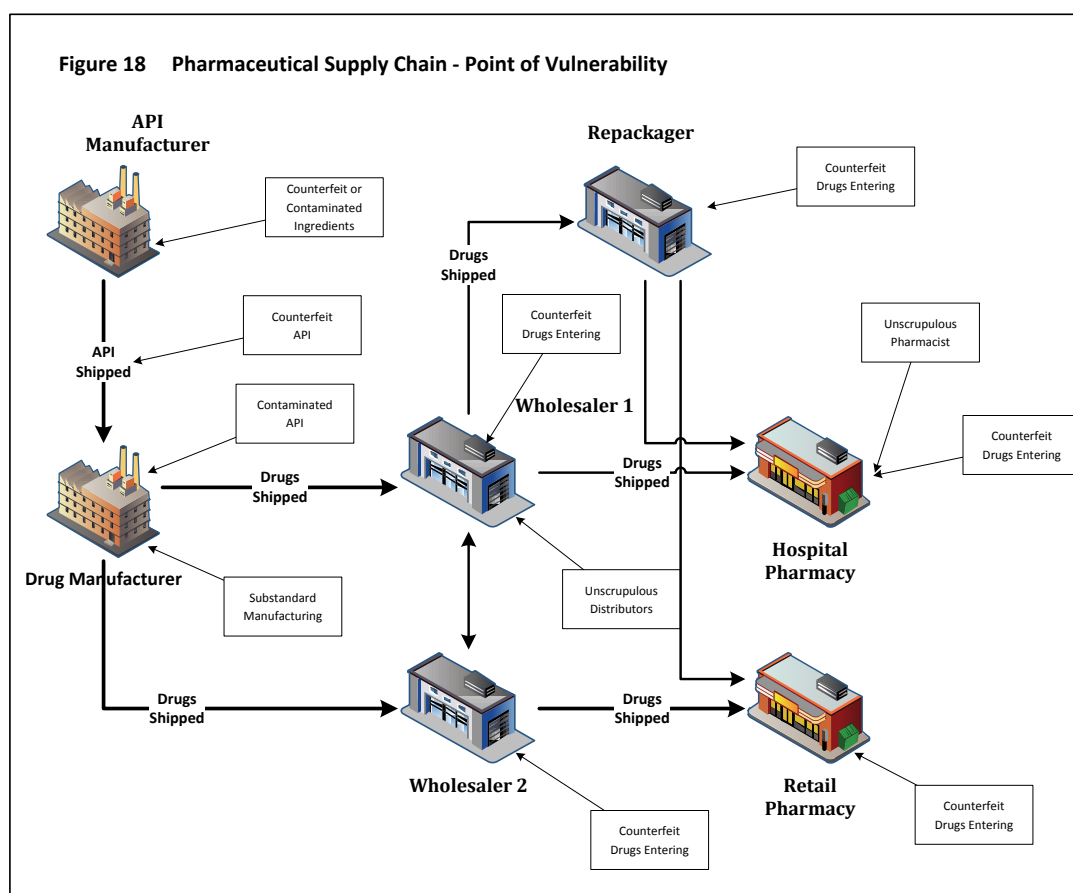
The reasons for low risk are the following:

- Little or no enforcement and penal sanctions (Davison, 2011; JDS Uniphase Corporation, 2013; World Health Organization, 2007)
- Little or no political will and commitment (Wertheimer & Wang, 2012; World Health Organization, 2007)
- Insufficient or appropriate drug legislation (World Health Organization, 2007)
- Missing or weak drug legislation (Wertheimer & Wang, 2012; World Health Organization, 2007)
- Bribery and conflict of interest (Bate, 2008; Wertheimer & Wang, 2012; World Health Organization, 2007)
- Complex pharmaceutical supply chain (Bate, 2008; Wertheimer & Wang, 2012; World Health Organization, 2007)

- Pharmaceutical medicines not regulated by the exporting country and within free trade zones (Wertheimer & Wang, 2012; World Health Organization, 2007)

2.5.3.5 How are Counterfeit Drugs Entering the Pharmaceutical Supply Chain?

The PSC is a very complicated logistic system. In the United States there are three basic models of PSC: the traditional wholesaler, the limited distribution model, and the direct distribution model. (see Figure 17) All three models start with the pharmaceutical manufacturer, who uses the API (raw material) to create drugs in their many forms. We start with the manufacturers and their API manufacturers to demonstrate how counterfeit drugs can enter the PSC from the API manufacturer. (See Figure 18)



The FDA reported in June 2011 that 80% of the pharmaceutical API and 40% of finished drugs are made outside of the United States (Nychis, 2011). With 80% of the

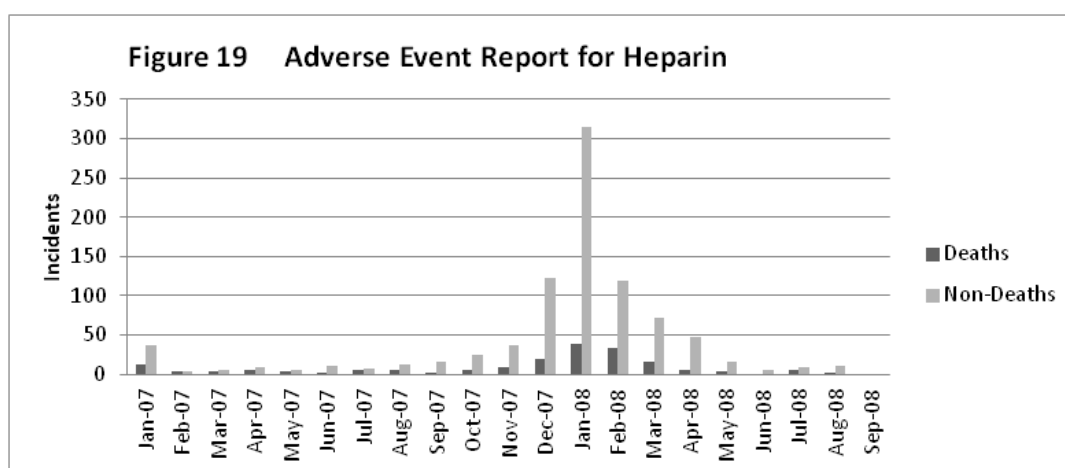
pharmaceutical API being made outside the U.S., it is easier for counterfeit API to enter the USPSC and ultimately make their way to the consumer. To prevent counterfeit API from entering the United States, the FDA performs inspections of the manufacturing API plants and the API is routinely tested by the drug manufacturers in the United States and abroad (Health Group, 2011; Usdin, 2009). Often, API testing technology is based upon 1950s technology that was established for off-patent drugs by the U.S. Pharmacopeial Convention (USP) (Health Group, 2011; Usdin, 2009). Another problem with oversea manufacturing API plants is the failure by the FDA to perform pre-inspection and timely inspections of these plants before allowing U.S. drug manufacturers to buy API from them (Harris, 2008; Usdin, 2009). The failure of the FDA to do a pre-approval inspection of the manufacturing API plant before giving their approval and the failure of the USP test to detect the contaminant in the API was the situation in the counterfeit heparin case.

Heparin is an anticoagulant drug that has been used since the 1930s (Briones, 2008). The majority of the world supply of heparin API is made in China and Baxter International Inc. was a major importer of the heparin API into the United States (Mintz & Liu, 2013) when suspicion about contaminated heparin manufactured by Baxter surfaced in Missouri around November 2007. By January 2008, some 50 reports of allergic reaction in six states came to the attention of the Center for Disease Control and Prevention (CDC). The FDA and Baxter had determined by the second week of January that the adverse reports were linked to nine lots of multi-dose heparin vials. On January 17, 2008 Baxter recalled the nine lots that appeared to be contaminated (Mintz & Liu, 2013; Usdin, 2009).

By the first of February, the CDC had reported 65 confirmed or probable cases of allergic reactions to Baxter heparin which indicated the earlier recall of the nine lots of heparin was not enough (Usdin, 2009). After confirming that other available sources of

heparin were not contaminated, a full recall of the remaining lots manufactured by Baxter was conducted on February 28, 2008. By March 2009, the FDA had received notices of 21 deaths and 785 adverse reactions to the contaminated heparin (Usdin, 2009).

The FDA discovered that twelve Chinese companies supplied the contaminated heparin to eleven countries (Kishimoto et al., 2008; Mintz & Liu, 2013; Usdin, 2009). PEW reported in 2011 that there were 178 deaths and 880 adverse reactions to the counterfeit drug from January 2007 to September 2008 (Health Group, 2011). (see Figure 19)



Source: After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs
Retrieved: June 27, 2014

The FDA tested the suspicious heparin according to approved methods, which were established by the USP in the 1950s, and all samples passed the tests for contaminants (Health Group, 2011; Usdin, 2009). This created the need to find another test(s) that would identify the contaminants in the heparin API. The FDA posted two new methods for testing the heparin API on March 6, 2008: capillary electrophoresis (CE) and nuclear magnetic resonance (NMR) spectroscopy (Usdin, 2009).

A task force was created to do the investigation with the FDA into the heparin contamination. On March 17, 2008, the FDA and the task force both agreed that oversulfated chondroitin sulfate (OSCS) was the contaminate in the heparin drug (Health Group,

2011; Kishimoto et al., 2008; Usdin, 2009). The new tests were followed by animal tests that verified the contaminant was responsible for the allergic effects displayed by the patients. Although the testing of contaminated heparin API was performed before manufacturing heparin, OSCS contaminate, a synthetic chemical, reacts similar to heparin and is why the previous test turned up negative for contaminates.

The contaminated supply of heparin in the U.S. only came from Baxter. Baxter's supplier of the heparin API was a company called Scientific Protein Laboratories LLC (SPL), which is a Wisconsin manufacturer of pancreatic enzymes and heparin. About half of the SPL heparin API was made by U.S. sources and the other half of the heparin API came from Scientific Protein Laboratories-Changzhou (SPL-CZ) in a joint venture with Techpool Bio-Pharma Co. Ltd. in China that began in 1999. The heparin API that came from Changzhou was tested and it was discovered that 20 out of the 24 samples were found to have an unidentified contaminant present (Usdin, 2009).

In 2004, Baxter began to buy the heparin API from SPL-CZ but failed to inspect the plant until 2007 because Baxter had relied upon earlier inspection results by a different company. In addition, the FDA had given Baxter permission to buy the heparin API from SPL-CZ because it had mistaken SPL-CZ for another company in its database. It was not until 2008 before the FDA realized its mistake and inspected the SPL-CZ plant. The FDA inspections of SPL-CZ found numerous problems including not having good manufacturing practices. As pointed out by the Germans who found contaminate heparin in PSC which did not come from SPL-CZ, the problem seems to be with the upstream Chinese suppliers who were consolidators and their sources, the raw material workshops.

In 2008, the FDA and Baxter both tried to inspect the consolidators and their raw material workshops but were not allowed to do so by the Chinese officials. Furthermore, the

Chinese officials have denied the contamination ever occurred. The FDA inspection on SPL-CZ reported that it had accepted material from unacceptable vendors and failed to identify contaminants in its heparin API supply which were found in more than half the heparin API lots.

The question is whether the heparin contamination was a problem of poor manufacturing practices or a deliberate act. Chondroitin sulfate (CS) is made from animal cartilage and OSCS is a modified form of CS; it mimics heparin which is made from pig intestines that are cooked, dried, and processed into heparin API. Since the source for heparin API and OSCS is different, it is viewed that the contamination of heparin API by OSCS was a deliberate act. In addition, OSCS is 99% cheaper than heparin API. The FDA viewed the OSCS contamination of the heparin API as a deliberate act because it took a level of sophistication and knowledge that OSCS would not show up on the routine test performed on the heparin API (Usdin, 2009).

Pharmaceutical manufacturers have been known to introduce counterfeit drugs into the PSC whether by using non-FDA approved overseas brokers or hiding the fact they were using undisclosed manufacturing sites. For example, in the late 1980s and early 1990s, Flavine International Inc. (US) company bought drugs from non-FDA approved Chinese plants (Department of Justice, 1997; PEW Trusts, 2014). In the 1990s an Italian pharmaceutical company, Biochimica Opos, a solely-owned subsidiary of the French drug company Roussel-Uclaf at that time, had undisclosed and unauthorized FDA manufacturing sites in Italy, France, and Romania producing antibiotic drugs for them (PEW Trusts, 2014). Biochimica Opos falsified records to hide where these drugs were being produced. In 2001, Roussel-Uclaf's successor Aventis Pharma AG pleaded guilty to multiple United States

felony charges for defrauding the FDA and paid a fine of \$33 million (PEW Trusts, 2014; Reuters, 2014).

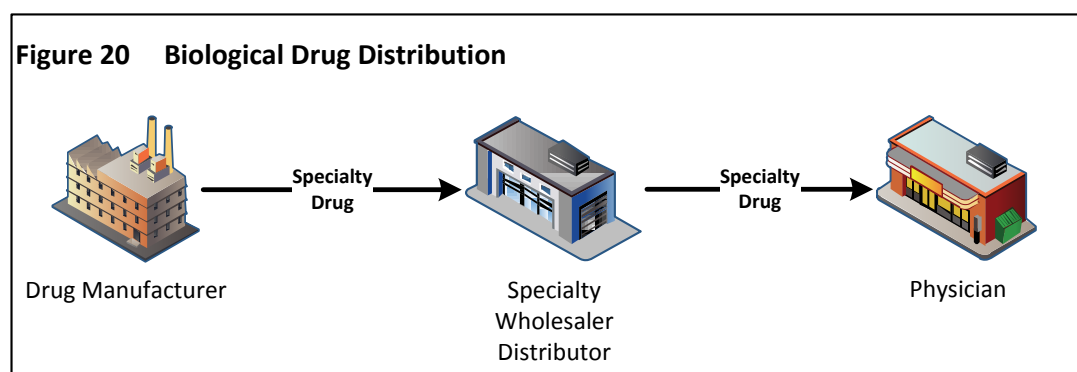
Another manufacturer, Ranbaxy Laboratory, had been supplying generic drugs to the U.S. for several years and had filled 52 million prescriptions in 2007 (PEW Trusts, 2014) when several safety and quality issues arose in 2008 after an inspection by the FDA of the Poanta Sahib and Dewas plants in India (FDA, 2013a). Ranbaxy Laboratory had used non-FDA approved manufacturing sites in obtaining their bulk API which resulted in the suspension of 30 Ranbaxy products from importation into the United States (FDA, 2013a; PEW Trusts, 2014). In 2013, Ranbaxy pleaded guilty and was fined \$500 million for three felony FDCA counts and four felony counts of providing false statements to the FDA in regards to their Paonta Sahib and Dewas plants in India (Brennan, 2013; Department of Justice, 2013). In addition, Ranbaxy admitted to manufacturing and releasing adulterated drugs from their Paonta Sahib plant in 2005 and 2006 (Brennan, 2013; Department of Justice, 2013). A suspension was again applied in 2014 to Ranbaxy's Laboratory Toansa plant in India and Ohm Laboratories plant in New Jersey which prohibited the plants from manufacturing and distributing APIs for FDA regulated drugs (FDA, 2014b).

The secondary wholesale distributors (non-ADR) are the biggest offenders of introducing counterfeit, diverted, and stolen drugs into the USPSC. We will not focus solely on the U.S. secondary wholesale distributors but worldwide secondary wholesale distributors as well. The following are examples of secondary wholesale distributors getting caught in the selling and distribution of counterfeit, diverted, and stolen drugs.

The first example of a corrupt secondary wholesale distributor has eleven individuals and three businesses involved in \$42 million worth of counterfeit Lipitor in 2005 (NABP, 2013). It was manufactured in Costa Rica and caused 18 million Lipitor tablets to be recalled

by a distributor. The counterfeit Lipitor and some misbranded Lipitor was smuggled into the U.S. from South America (NABP, 2013).

The next example is the drug Avastin which was counterfeited overseas and brought into the USPSC through secondary wholesale distributors. Avastin is a biologic that treats cancer. Since it is a biologic, a physician will order Avastin from a specialty wholesale distributor. (see Figure 20)



Counterfeit Avastin was found in a warehouse in Syria in 2009 (Blair, 2012; Faucon & Whalen, 2012) and in Shanghai in 2010 (Faucon & Whalen, 2012). In early 2012, a batch of counterfeit Avastin that contained zero API and consisted of starch, salt, a cleaning solvent, and other chemicals reached the United States (Weaver & Whalen, 2012). The supply route for the counterfeit Avastin may have begun in China and next to Egypt, then onto a wholesale distributor in Switzerland where the paper trail begins (Faucon & Whalen, 2012). Then we can follow it to wholesale distributors in Denmark, Great Britain, Canada, and the United States (Montana, Tennessee) (Faucon & Whalen, 2012; Weaver & Whalen, 2012). The counterfeit Avastin ended up in Los Angeles, CA at a physician's office (Blair, 2012). The batch numbers were B6010, B6011, and B86017 and labeled as being manufactured by Roche (FDA, 2012b) instead of Genentech (FDA, 2012b).

A second batch of counterfeit Avastin was found that was part of the first reported counterfeit in February 3, 2012 (FDA, 2012a). This time the drug name on the container was Altuzan which is the Turkish version of Avastin (RX-360, 2014). The batch number was B6021 (FDA, 2012a). This batch came from Richards Pharma, aka Richards Services, Warwick Healthcare Solutions, or Ban Dune Marketing Inc. (FDA, 2012a).

A third batch of counterfeit Avastin (Altuzan) was found in the U.S. in 2013 and was distributed by Medical Device King, aka Pharmalogical, and Taranis Medical. The batch numbers were B6022B01 with an expiration date of November 2013 and B6024B01 with an expiration date of February 2013 (FDA, 2013b). This was the first time a U.S. drug distributor had been implicated in the distribution of counterfeit drugs.

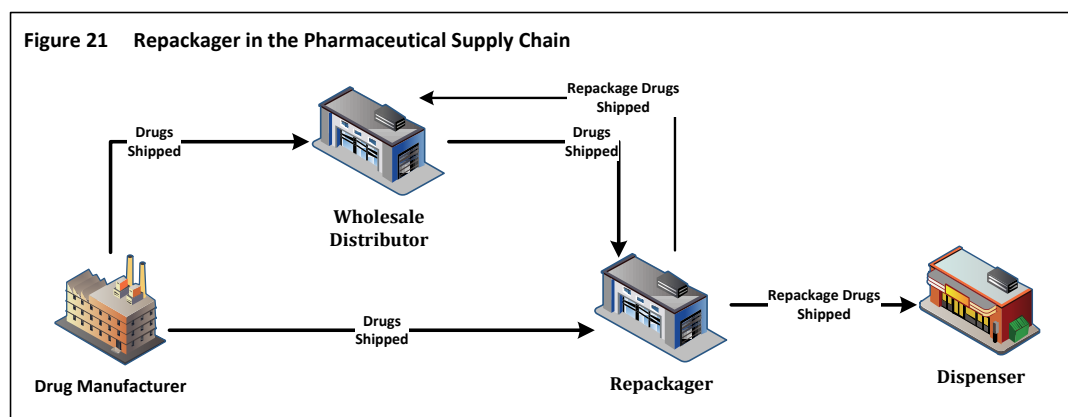
The examples of the counterfeit Avastin and Lipitor had to do with obtaining drugs from outside of the U.S. for a cheaper price and very corrupt wholesale distributors. Although the Swiss, Danish, and British wholesale distributor companies were involved, all signs point to organized crime as being behind these counterfeit drugs.

Although the next examples do not involve counterfeit drugs, they do involve corrupt wholesale distributors along with stolen and then diverted drugs worth over \$1 billion (NABP, 2013). The first case began in July of 2012 when 48 individuals had federal criminal charges filed against them for the diversion of drugs for Medicaid patients. The drugs were sold back to the pharmacies through corrupt wholesale distributors which resulted in the fraudulent Medicaid reimbursement payments of over \$500 million (NABP, 2013). The FDA Office of Criminal Investigation was involved in the second case, where twenty-three individuals and three corporations were involved in a diversion scheme that crossed several states and totaled more than \$600 million. This second case covers the years of 2007 through 2011, where the defendants supplied diverted drugs with fake pedigrees to

chain and independent pharmacies all over the country (NABP, 2013). The pharmacies that received the diverted drugs had no idea of their origin and quality because the false pedigrees made it virtually impossible to trace.

The repackager's role in the PSC is to take a large number of items per container and break them down to a smaller number of items per container and sell them back to the wholesale distributor or to the dispensers (UNICRI, 2013). Repackagers can be importers of drugs from outside as well as inside the United States (United Nations Office on Drugs, 2010). (see Figure 21) Repackaging is another source of counterfeit drugs being introduced into the USPSC. Importers can import counterfeit drugs and repackage them into legitimate packages and to enter them into the USPSC (Davison, 2011). Repackagers could be legitimate pharmaceutical companies during the day and counterfeiters at night (United Nations Office on Drugs, 2010). This technique is used for the more difficult drugs to counterfeit such as biologics (United Nations Office on Drugs, 2010) and for the adulteration of boxes (UNICRI, 2013). The adulteration of boxes is linked to incorrect dosage and expiration dates (UNICRI, 2013).

In 2006, there were 26 incidents of counterfeit biologics in the world as reported by PSI (Finlay & Center, 2011). Because biologics are administered via injections or intravenously, counterfeit biologics are often repackaged into legitimate containers with legal labels which make them harder to detect as counterfeit (United Nations Office on Drugs, 2010).



For example, in 2003 three individuals were apprehended for the illicit sale and distribution of counterfeit Procrit, a prescription biological drug of Amgen which is administered via injection (Finlay & Center, 2011). In 2006, counterfeit Fluarix, an influenza vaccine, was found circulating throughout Brazil by Brazilian authorities (Finlay & Center, 2011). In 2009, immunoglobulin vials that were imported from China and repackaged under a leading brand name were seized as being counterfeit. In 2013, an importer was sentenced to two years in federal prison for buying an assortment of drugs from Turkey, India, and Pakistan from unapproved FDA sites, shipping them to California, repackaging the drugs, and then shipping them to doctors in California, Florida, Texas, and elsewhere for more than \$7 million (NABP, 2014b).

Another way for counterfeit drugs to enter the PSC is from unscrupulous pharmacists, physicians, nurses, and other medical personnel. For example, a pharmacist who was an owner of two pharmacies diluted some 98,000 prescriptions from 400 doctors from November 2000 to May 2001 in Kansas City, MO (Belluck, 2001; Elliot, 2002). A nurse injected AIDS patients with tap water instead of the Schedule II narcotics to satisfy her drug habit (Inciardi, Surratt, Kurtz, & Burke, 2006). There have also been several occurrences of drug diversion by other medical personnel in the U.S. where unused drugs

were bought from patients, repackaged, and then sold back to the corrupt or unsuspecting pharmaceutical wholesalers (NABP, 2014a; NABP, 2014c; Vivian, 2013). These drugs could have been expired or contaminated. Drug diversion in 2012 cost the New York Medicaid program \$500 million and put Medicaid patients in risk (NABP, 2013).

2.6 Anti-Counterfeit Technologies

Anti-Counterfeit Technologies (ACTs) are one of many methods to combat counterfeit drugs from entering the PSC. There are other methods such as legal actions against the perpetrators, consumer education and information, private investigations, and cooperation between law enforcement agencies (Bansal, Malla, Gudala, & Tiwari, 2013). Many, if not all, of these methods have been implemented to different degrees of success. ACTs are constantly changing as new counterfeit methods are discovered and understood. ACTs are broken down into two methods: product authentication and product track-trace (Davison, 2011).

2.6.1 Product Authentication

Drug manufacturing is more than the drug composition as it entails drug label, container, pill or tablet size, shape, color, package, lot number, and expiration date (Davison, 2011). All of these are copied in an attempt to introduce the counterfeit drug into the PSC. To combat copying the features of the drug, techniques like those used in paper money are used to make it difficult to copy these features of a manufactured drug. So, like paper money, there are many ways to authenticate the drug.

Authenticate technologies (ATs) are broken down into two groups: digital and physical (Davison, 2011). Once the person is educated on what to look for, a physical examination of containers, pill, tablet, or liquid becomes a powerful tool in ATs (Wertheimer

& Wang, 2012). Digital authentication is the assignment of digital data to the container(s) which can be processed by a computer. Both of these ATs contain overt and covert technologies.

Making tablets or pills harder to copy is like making paper money harder to counterfeit. This means a pill or tablet should be a unique size, shape, color, and granularity and adding embossing, debossing, printing, and surface marking (Davison, 2011; Power, Unknown). Once you understand what physical traits (on-dose features) have been applied, then it's easy to physically authenticate the drug. However, organized crime could copy most of these features which would defeat their use. In addition, once the tablet or pill is in the bottle there is very unlikely chance there will be random sampling during transport to validate the drug. This would leave it to the pharmacist to validate the drug at the pharmacy when the pills or tablets are removed from the transport bottle to the prescription bottle..

By inserting an inert substance(s) into the API, the API or drug compound will be harder to counterfeit. The FDA has a list of Inactive Ingredients Guide (IIG) and "generally recognized as safe" (GRAS) additives (Davison, 2011; Wertheimer & Wang, 2012). If used in combination, they can make unique markers in the drug compound or API, making it harder to counterfeit the API or drug compound. However, this would require special equipment to detect the markers in the drug. Once the pill or tablet is in the transport container to the wholesaler, it is highly unlikely the transport bottles will be sampled or scanned. Once again, the final determination of the drug authentication would belong to the pharmacist

There are tests used to verify drugs. There are destructive and nondestructive tests (Davison, 2011). Destructive test means a sample has to be removed from its package and prepared in way as to make the sample unable to be returned to its state before testing. Destructive tests are further broken down to simple and laboratory tests. The simple

chemical and physical tests are colorimetry, hardness and dissolution, thin layer chromatography (TLC), ultraviolet and visible spectroscopy (Davison, 2011; Wertheimer & Wang, 2012). The laboratory tests are atomic absorption spectrophotometry (AAS), X-ray techniques, nuclear magnetic resonance (NMR) spectroscopy, mass spectrometry (MS), gas chromatography (GC), liquid chromatography (LC), capillary electrophoresis (CE), and forensic palynology (Davison, 2011; Wertheimer & Wang, 2012). Since many of these techniques make the package or samples taken unsalable, these techniques are used for secondary analysis. Nondestructive techniques have been developed for field testing and to be used as primary means of testing. The nondestructive methods are portable X-ray diffraction, infrared spectroscopy, and terahertz imaging (Davison, 2011; Wertheimer & Wang, 2012).

As we know from the Tylenol incident, primary container security can be the key to reducing counterfeit drugs from entering a market. Since the Tylenol incident, several OTC drugs have been fitted with tamper resistance seals in an attempt to indicate to the consumer whether the drug has been modified which allows the consumer to report the tampering (Shah, Prajapati, & Agrawal, 2010). There are many other primary package security methods that can be applied, including package design, printing, labels, holograms, and diffractive optically variable image devices (DOVIDs) (Davison, 2011; Shah et al., 2010). Furthermore, there are specialty inks, covert taggants, and forensic markers (Wertheimer & Wang, 2012). One or more of these techniques are usually applied to the drug container.

2.6.2 Product Track-Trace

We all know about product tracking from our ordering of goods on the Internet and their delivery to our home or office. We can go on the Internet to sign into the shipping

company or the ordering company and track our package to find its location and delivery time. So, how are these products tracked?

Products are tracked through a serial or identification number which is read, inserted, and updated into a computer system containing a database. The act of logging into the seller or shipping company computer system allows us to access the location of product through the serial or identification number. International Standard Serial Number (ISSN) is another one standard for serial numbers given to print and electronic media such as journals, newspaper, magazine, etc. (ISSN, Unknown). Stock keeping unit (SKU) is another standard serial number.

One of the earliest adoptions of linear barcodes was for tracking library products. Used in large public and academic libraries, linear barcodes were cheap to print and easy to read for tracking books to ensure proper turnaround (Anonymous, 2012). The information on a barcode has many standards and the code is referred to as symbology (Anonymous, 2012). There are about 20 standard symbologies being used such as UPC, EAN, ISBN, and PDF 417 (Yam, Takhistov, & Miltz, 2005). UPC stands for “Universal Product Code”, was introduced in the 1970s, and is primarily used by grocery stores for inventory, stock reordering, and checkout (Yam et al., 2005). Barcodes are optically scanned using a laser requiring line of sight of the barcode or magnetically scanned using a swipe reader (Anonymous, 2012).

Linear barcodes are limited in size and the amount data stored (Yam et al., 2005). Technology has been improving and the need to store more information on a barcode is becoming more acute. New barcodes have been developed to store more information. One of these new standards is PDF 417, where PDF stands for Portable Data File (Yam et al., 2005). PDF 417 is a 2-dimensional barcode with a capacity of a few bytes to 2 kilobytes

(Anonymous, 2012). Another 2-D matrix barcode standard is ECC200 which is the standard that GS1 uses (GS1, Unknown; TEC-IT, 2014).

Radio frequency identification (RFID) is another way to store and retrieve information about a product. RFID is able to read/write information to or from the tag through a reader like a linear barcode reader except it uses radio frequency (Davison, 2011). The tag consists of an antenna and a chip where the information is stored. The tag can be active, passive, or semi-passive (Kabachinski, 2005). An active tag has a battery which makes it a larger and a more expensive tag as compared to a passive tag (Want, 2006). The tag is attached to the item or package.

There are low (<135 KHz, ~18"), high (13.56 MHz, ~3'), ultrahigh (890-930 MHz, ~15 to ~30'), and microwave (2.45 GHz, ~3') frequency tags and readers (Kabachinski, 2005). The higher the frequency of the tag, the higher the read rates. The read range of each tag is related to the higher frequency range except for microwave where the read range is similar to the HF tags (Kabachinski, 2005). The tag classes are 0 through 4 with tag class 0 being read-only tags preprogrammed at the manufacturing plant. Tag class 4 are read/write tags and have integrated transmitters that can communicate with other tags and devices. Tag class 1 is a write-once tag that can be written to once by the manufacturer or user and can be read multiple times. Tag class 2 is a read/write tag with more memory and can be written to multiple times by manufacturer or user. Tag class 3 is a read/write tag that can contain onboard sensors.

Another method of knowing something about an object is to know its history, such as where an object originated and where it has been. In the art world this is known as provenance and in the breeding world it is known as a pedigree. A pedigree provides a

history of the animal and its origins. This is product tracing as the pedigree accompanies the animal from buyer to seller and so forth.

By attaching a serial number to an object and recording on paper or in an electronic format the object's serial number, origin and owners, we have created a pedigree for that object. When we receive this object, we will know its provenance or pedigree. The cost of the pedigree is spread from buyer to seller and so forth which makes it practical for real-time access and it does not require a database for storage. However, as we know from in the art and breeding world, pedigrees can be faked and the product the pedigree is supposed to represent is counterfeit.

2.7 Pedigree System

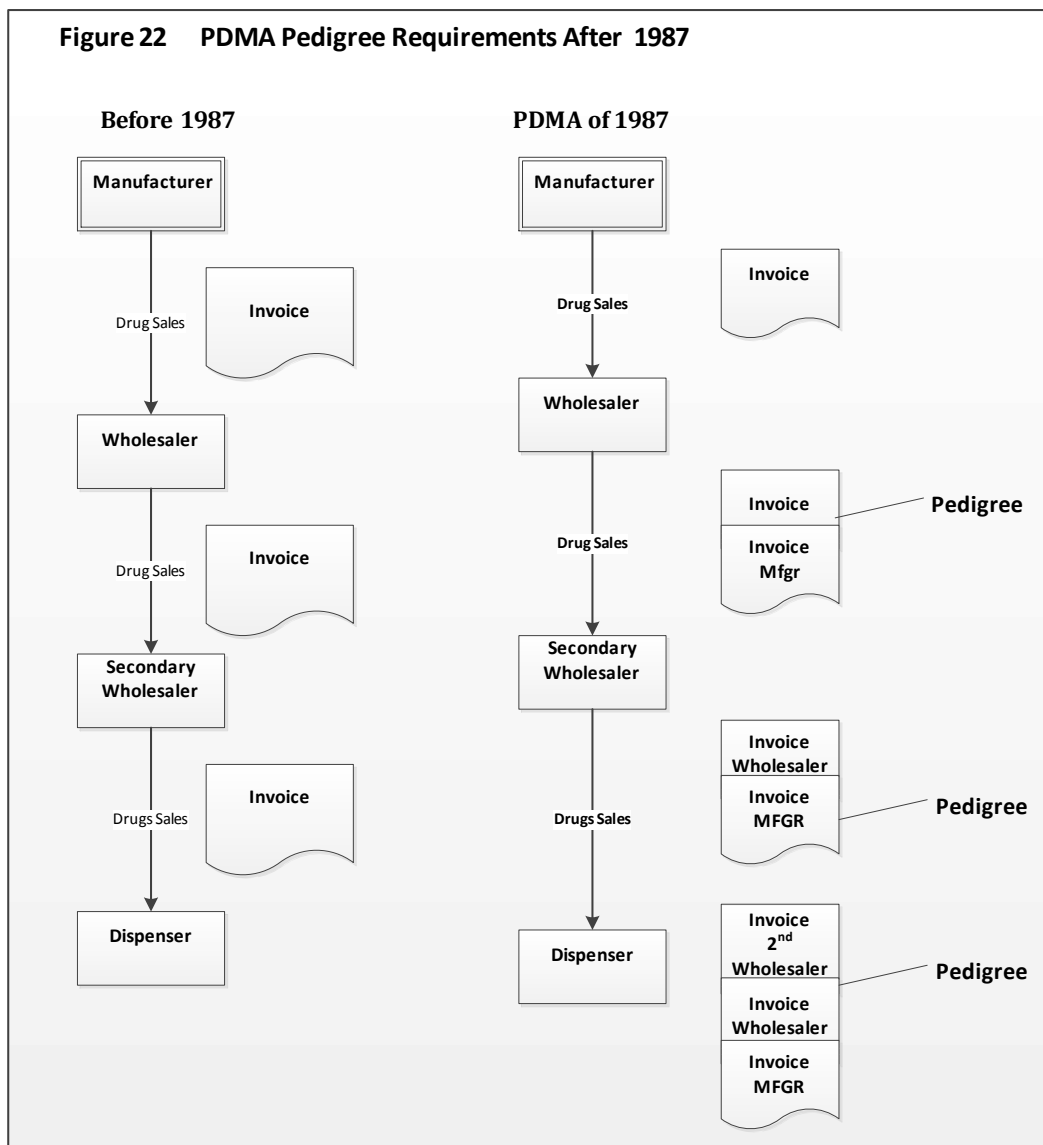
Before 1987, there were five days of a Congressional hearing that resulted in a subcommittee formal report with the following concerns:

- the existence of a drug wholesale submarket prevents knowing the source of the drug (Drabiak, 2005);
- subpotent or adulterated drugs may enter the USPSC through the reimportation of drugs (Drabiak, 2005);
- manufacturer representative's free samples to physicians may encourage drug adulteration and/or misbranding (Drabiak, 2005);
- health care institutions are releasing drugs into the market which could encourage drug diversion (Drabiak, 2005);
- persons from foreign countries are counterfeiting brand name drugs which promotes subpotent and impotent drugs that compete with American market and tarnish the good name of legitimate products in those countries (Drabiak, 2005).

The result of the report was the passing of The Prescription Drug Marketing Act of 1987 (PDMA). PDMA was proposed based upon those hearings and signed into law on April 22, 1988 by the president. In the United States, PDMA was the first attempt to secure the PSC. A part of the PDMA was to initially establish a federal pedigree program which was to be administered by the FDA.

Before 1987, each transaction would only include the current sales information and none of the sales history information. So by the secondary wholesaler there was no record where the drugs came from. PDMA required a sales transaction history to accompany the drugs that were being bought which created the sales history or pedigree for the drugs being bought (Thaul, 2013). (see Diagram 2)

Due to industry objections, the FDA delayed the effective date of the PDMA of 1987 regulations for several years until December 2006 (NABP, 2013). Because the federal pedigree program was delayed, the states started to require stronger laws in regards to their PSC (NABP, 2013). In 1992, Florida created its own pedigree system and requirements (Stovall, 2006). However, counterfeit drugs continued to be a problem in Florida (Stovall, 2006) and the Florida legislation created the Prescription Drug Protection Act (FPDPA) of 2003 based on the recommendations of a grand jury convened by then Governor Bush. FPDPA was amended in 2005 to allow electronic as well as paper pedigrees and its final act was to take effect on July 1, 2006 (Stovall, 2006).



Source: <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAAct/SignificantAmendmentstotheFDCAAct/PrescriptionDrugMarketingActof1987/ucm256466.htm>
Retrieved: July 1, 2014

After much delay and with the Florida experience with corrupt wholesale distributors in 2003, the FDA announced in 2006 that it would require pedigrees from the wholesalers starting on December 1, 2006 (Young, 2006). There were objections to the pedigree requirement by a group of wholesalers known as the RxUSA. A federal rule and some states regulations did not require an authorized distributor of record (ADR) to provide a pedigree to their buyers. This meant the primary wholesalers were not required to supply a pedigree

to the secondary wholesalers. This would have created a situation where the secondary wholesalers were required to give their buyers a pedigree which they did not have, which created an impasse. The pedigree requirement of the PDMA for secondary wholesalers would have put thousands of them out of business. Thus, on December 5, 2006 a federal district court judge delayed the implementation of the federal pedigree for the above reasons.

Meanwhile in other states, by 2012 twenty-nine states had adopted, proposed, or enacted state or board regulations in regards to the use of drug pedigrees (HDMA, 2014). In addition, 18 states had enacted drug pedigrees. In 2004, California passed a pedigree law that would have an effective date as January 1, 2005 and two enactment dates (Messplay, 2014). The first enactment date was January 1, 2007 for wholesale distributors and January 2008 for the pharmacies of the state. Under the California law, the pedigree would be electronic, manufacturers would initiate the pedigree, and the pedigree to be serialized, and no manufacturer or wholesaler or pharmacist would be allowed to buy or sell drugs without a pedigree.

Because of industry input, the California legislators passed multiple delays of pedigree law implementation until 2016 and 2017 which were the final dates. In addition, in March 2007 California's Board of Pharmacy stated that the GS1 EPCglobal Drug Pedigree Standard meets the requirements of the California pedigree law (Messplay, 2014). Thus, GS1 Drug Pedigree Messaging Standard (DMPS) based on XML language became the standard because all drugs coming in and going out of California required a pedigree (EPCglobal, 2007).

The Food and Drug Administration Amendments Act of 2007 (FDAAA ; Public Law 110-85) allows the FDA to set standards for identification, validation, authentication, track and trace of prescription drugs but not the authority to require it (U.S.

GOVERNMENT PRINTING OFFICE, 2013). The Food and Drug Administration Safety and Innovation Act (FDASIA, Public Law 112-144) of 2012, under Title VII, provided the FDA the authority that requires domestic and foreign drug manufacturers that sell pharmaceutical drugs and devices in the United States to register and be inspected by the FDA. The registration of domestic and foreign manufacturers required an electronic database to be created to maintain the registration information of the manufacturers. In addition, the FDA was given the authority to refuse the import by foreign or domestic manufacturers if inspections of their manufacturing facility was delayed, limited, or denied.

This lasted until November 27, 2013, when the Drug Quality and Security Act (DSQA, Public Law 113-54) (Upton, 2013) was signed by the U.S. president. Since DSQA is the law in all states, we will focus our attention on Title II of the DSQA which is called Drug Supply Chain Security Act (DSCSA, Sec. 201). The DSCSA is a pedigree and product identifier verification system. The following will be a discussion of the DSCSA analysis, modeling, and proposed implementation.

3. DSCSA Analysis, Modeling, and Implementation

Since DSCSA will replace all other track, trace, and pedigree systems in the United States, especially the California pharmaceutical drug E-Pedigree system {DSCSA sec 585 (a)}, we will focus our attention on DSCSA and determine the approach that will be taken by this act. DSCSA gives the FDA the authority to build an interoperable system to trace pharmaceutical products in the USPSC within ten years after the enactment of the DSCSA which was November 27, 2013.

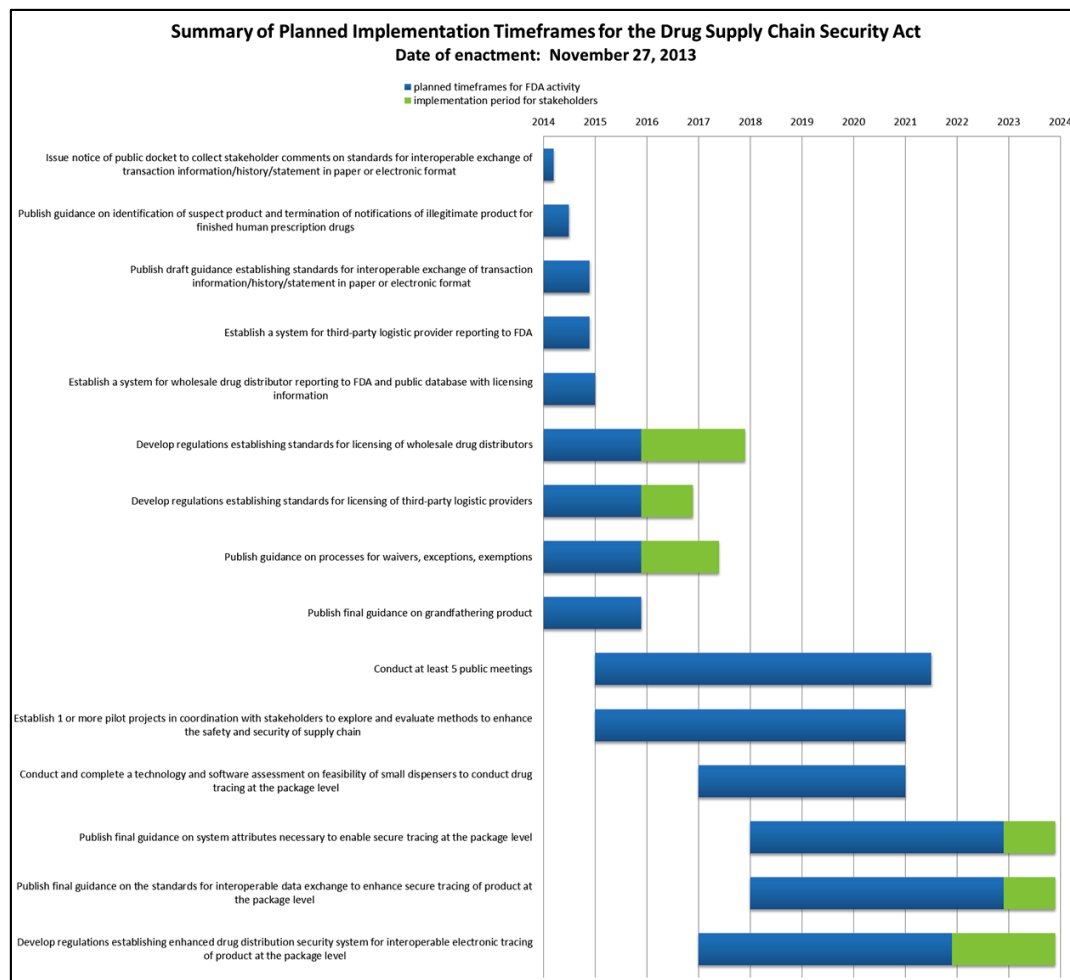
3.1 DSCSA Requirements

DSCSA is in its beginning stage of development as the FDA completed its first required task of the act by gathering comments from stakeholders and pharmaceutical community which was completed on April 21, 2014. The second task completed by the FDA was the public guidance document published in June 2014 to support the identification of illicit products and notification. The FDA is to complete the third task by November 2014, which is the published draft guidance document that provides standards for the interoperable exchange of transactional information, history, and statement in paper or electronic form. There are many more requirements due by January 1, 2015 by all trading partners which will be explained later. The FDA will establish a database for the purpose of registering wholesale distributors by January 1, 2015. Other tasks of note are the pilot programs that can begin after January 1, 2015.

The analysis of the USPSC under the DSCSA will be conducted at a high level depicting the forward flow of the products and the requirements dictated by the DSCSA. It is beyond the scope of this thesis to do an exhaustive depiction of the effects on the USPSC by the DSCSA as the regulations have not yet been formalized and therefore subject to

change. The following image is a project plan indicating the high level tasks that are to be completed by the FDA and stakeholders according to the DSCSA. (see Figure 23)

Figure 23



Source: <http://www.fda.gov/drugs/drugsafety/drugintegrityandsupplychainsecurity/drugsupplychainsecurityact/ucm382022.htm>

Retrieved: July 1, 2014

3.2 DSCSA Definitions

There are many definitions in the DSCSA. DSCSA definitions are found in the DSCSA Section 581. In the following definitions, we explain the major definitions of this act and leave the rest to the reader. We start with the trading partner definition as it sets the scope of the act. All references are from the DSCSA document.

DSCSA defines USPSC trading partners. DSCSA requires all trading partners to be registered by the state or by the U.S. government (FDA). In addition, all trading partners in the USPSC can only do business with other trading partners who are authorized by being registered by the state or by the FDA {sec. 581(2)}. This requirement will make the USPSC a closed system.

The trading partners of the USPSC are defined to be manufacturer, wholesale distributor, third-party logistics provider (3PLs), repackager, and dispenser {sec. 581(23)}. Authorized distributor of record (ADR) is defined to be "those distributors with whom a manufacturer has established an ongoing relationship to distribute such manufacturer's products" (2013, sec. 583 (b)). Wholesale distributors can be ADR and non-ADR. Dispensers are defined as retail pharmacy, hospital pharmacy, and a group of chain pharmacies under common ownership and control that don't act as a wholesale distributor and exempts a person who dispenses only products used by animals {sec. 581(3)}.

A manufacturer is defined to be

- "a person that holds an application approved under section 505 or a license issued under section 351 of the Public Health Service Act for such product, or if such product is not the subject of an approved application or license, the person who manufactured the product;" (2013, sec. 581(10)(A))
- "a co-licensed partner of the person described in subparagraph A that obtains the product directly from a person described in this subparagraph or subparagraph A. or C.; or" (2013, sec. 581(10)(B))
- "an affiliate of a person described in subparagraph A. or B. that receives the product directly from a person described in this subparagraph or subparagraph A. or B." (2013, sec. 581(10)(C)).

A repackager is defined to be "a person who owns or operates an establishment that repacks and relabels a product or package for" (2013, sec. 581(16)) "further sale; or" (2013, sec. 581(16)(A)) "distribution without a further transaction" (2013, sec. 581(16)(B)).

Wholesale distributors are defined by the individual state laws. DSCSA has placed restrictions on who can be an owner of a wholesale distributor business. "The standards established under subsection (a) shall include requirements to prohibit a person from receiving or maintaining licensure for wholesale distribution if the person" (2013, sec. 583(d))

- "has been convicted of any felony for conduct relating to wholesale distribution, any felony violation of subsection (i) or (k) of section 301, or any felony violation of section 1365 of title 18, United States Code, relating to product tampering; or" (2013, sec. 583(d)(1))
- "has engaged in a pattern of violating the requirements of this section, or State requirements for licensure, that presents a threat of serious adverse health consequences or death to humans" (2013, sec. 583(d)(2)).

From above, we have defined the main trading partners. The following are the definitions needed to further define the requirements of the USPSC under the DSCSA. DSCSA will define product and the product identifier used to verify the product. DSCSA will define the following: standard numerical identifier (SNI), package, smallest saleable unit, homogenous case, transaction, transaction statement, history, and information. The following will cover the DSCSA definitions of affiliate, suspect product, illegitimate product, and to verify or verification.

A product identifier is defined as

a standardized graphic that includes, in both human-readable form and on a machine-readable data carrier that conforms to the standards developed by a widely recognized international standards development organization, the standardized numerical identifier, lot number, and expiration date of the product (2013, sec. 581(14)).

Product identifiers will be a part of the 1-D and 2-D data matrix barcode when affixed to or imprinted upon a package or homogenous case.

Basically, a product means a prescription drug in its final form, such as a tablet or capsule that would be given to a patient for consumption. All other prescription drugs defined as biologics, blood or blood components, radioactive drugs, imaging drugs, intravenous drugs, any medical gas, etc. are excluded. A more complete definition of "Product" can be found in {sec. 581(13)}.

S standard numerical identifier (SNI) is defined to be:

a set of numbers or characters used to uniquely identify each package or homogenous case that is composed of the National Drug Code that corresponds to the specific product (including the particular package configuration) combined with a unique alphanumeric serial number of up to 20 characters (2013, sec. 581(20)).

A package is defined to be "the smallest individual saleable unit of product for distribution by a manufacturer or repackager that is intended by the manufacturer for ultimate sale to the dispenser of such product" (2013, sec. 581(11)(A)).

A smallest saleable unit is defined as "the smallest container of product introduced into commerce by the manufacturer or repackager that is intended by the manufacturer or repackager for individual sale to a dispenser" (2013, sec. 581(11)(B)).

A homogenous case is defined to be "a sealed case containing only product that has a single National Drug Code number belonging to a single lot" (2013, sec. 581(7)).

A transaction is defined to be "the transfer of product between persons in which a change of ownership occurs" (2013, sec. 581(24)(A)).

Transaction history is defined as "a statement in paper or electronic form, including the transaction information for each prior transaction going back to the manufacturer of the product" (2013, sec. 581(25)).

Transaction information is defined by {2013, sec. 581(26)} to be the following:

- "the proprietary or established name or names of the product;" (2013, sec. 581(26)(A))
- "the strength and dosage form of the product;" (2013, sec. 581(26)(B))
- "the National Drug Code number of the product;" (2013, sec. 581(26)(C))
- "the container size;" (2013, sec. 581(26)(D))
- "the number of containers;" (2013, sec. 581(26)(E))
- "the lot number of the product;" (2013, sec. 581(26)(F))
- "the date of the transaction;" (2013, sec. 581(26)(G))
- "the date of the shipment, if more than 24 hours after the date of the transaction;" (2013, sec. 581(26)(H))
- "the business name and address of the person from whom ownership is being transferred; and" (2013, sec. 581(26)(I))
- "the business name and address of the person to whom ownership is being transferred" (2013, sec. 581(26)(J)).

Transaction statement is defined as "a statement, in paper or electronic form, that the entity transferring ownership in a transaction—" (2013, sec. 581(27))

- "is authorized as required under the Drug Supply Chain Security Act;" (2013, sec. 581(27)(A))
- "received the product from a person that is authorized as required under the Drug Supply Chain Security Act;" (2013, sec. 581(27)(B))
- "received transaction information and a transaction statement from the prior owner of the product, as required under section 582;" (2013, sec. 581(27)(C))
- "did not knowingly ship a suspect or illegitimate product;" (2013, sec. 581(27)(D))
- "had systems and processes in place to comply with verification requirements under section 582;" (2013, sec. 581(27)(E))
- "did not knowingly provide false transaction information; and" (2013, sec. 581(27)(F))
- "did not knowingly alter the transaction history" (2013, sec. 581(27)(G)).

One of the exceptions to the above transaction statement definition is when the wholesale distributor has purchased the product directly from the manufacturer, the transaction statement will "state that such wholesale distributor, or a member of the affiliate of such wholesale distributor, purchased the product directly from the manufacturer, exclusive distributor of the manufacturer, or repackager that purchased the product directly from the manufacturer" (2013, sec. 582(c)(1)(A)(ii)(I)(aa)(AA)).

Affiliate is defined as "a business entity that has a relationship with a second business entity if, directly or indirectly:" (2013, sec. 581(1))

- "one business entity controls, or has the power to control, the other business entity; or" (2013, sec. 581(1)(A))
- "a third party controls, or has the power to control, both of the business entities" (2013, sec. 581(1)(B)).

Verification or verify is define as

determining whether the product identifier affixed to, or imprinted upon, a package or homogeneous case corresponds to the standardized numerical identifier or lot number and expiration date assigned to the product by the manufacturer or the repackager, as applicable in accordance with section 582 (2013, sec. 581(29)).

Suspect product is defined to be a product that is potentially counterfeit, diverted, stolen, or adulterated and may have been part of fraudulent transactions or basically unfit for distribution due to adverse health consequences or death to humans {2013, sec. 581(21)}.

Illegitimate product is defined to be counterfeit, diverted, stolen, or intentionally adulterated and has been part of fraudulent transactions or basically unfit for distribution due to adverse health consequences or death to humans {2013, sec. 581(8)}.

For the sake of convenience, I will define transaction records to be transaction statement, transaction information, and transaction history.

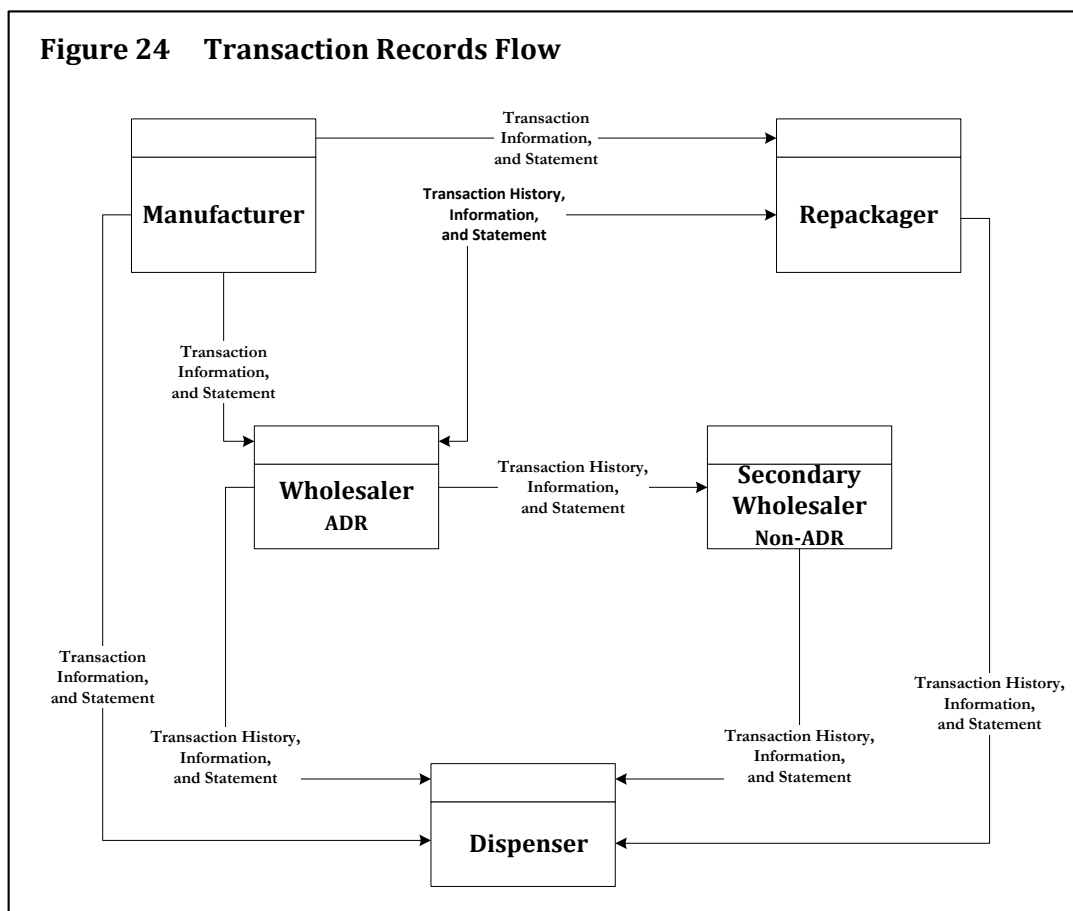
3.3 Trading Partners Registrations and License

According to Title VII of The Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA, Public Law 112-144), within a two year period after July 9, 2012, all domestic and foreign manufacturers doing business in the U.S. have to be registered and provided a facility identifier by the FDA. According to {sec 584(a)}, all 3PLs doing business in the USPSC will be license by the state {sec 584(a)(1)(A) or by the FDA by the beginning

of November 2014 {sec. 584 (b)} and all wholesale distributors doing business in the USPSC will report to the FDA to be registered by the beginning of January 1, 2015. {sec. 204 (a)(2)(B)} If the state doesn't register 3PLs, then the FDA will provide a license for the 3PLs. {sec. 584(a)(B)} All dispensers are to be registered by the state {2013, sec. 581(9)(C)}.

3.4 Product Tracing Systems Requirements

The wholesale distributor, dispenser, and secondary wholesale distributor will have a transaction records storage system. The transaction records storage system can be an electronic database. The electronic database can be used to store transaction statement (TS), information (TI), and history (TH) for each transaction for the purpose of verification of a product. The manufacturer and repackager will have a transaction records and product identifier storage systems for the purpose of verification of a product {2013, sec. 581(27)(E)}. Figure 24 is a logical model of this system.



3.5 Transaction Records and Product Identifier Requirements

3.5.1 Manufacturer

In the case where the product and transaction records trail begins with the manufacturer, it only makes sense that the TH would only contain current TS and TI that will be sent in a single document to the recipient of the shipment of products from the manufacturer {2013, sec. 582(b)(1)(A)(i)}. However, by no later than January 1, 2015, the manufacturer is not allowed to accept ownership of any product without the transaction records on or before taking ownership and only from authorized trading partners {sec. 582(c)(1)(A)}. All transaction records maintained by manufacturers must be kept for a period of six years {sec. 582(b)(1)(A)(ii)}.

Manufacturers will have systems in place by January 1, 2015 to allow for verification of suspect products or a verification requested by the Secretary of Health and Human Services (Secretary) or other Federal or State official for products that has been determined to be in their possession or control {sec. 582(b)(4)} or into the investigation into possible suspect products. The investigational records of a suspect product will be kept for a period of six years after the conclusion of the investigation {sec. 582(b)(4)(A)(iii)}. An electronic database can be used to maintained the transaction records for verification purposes {2013, sec. 582 (b)(4)(D)}.

By November 2017, manufacturers will provide an electronic format of the transaction records {2013, sec. 582(b)(1)(C)(i)}, The exception is that the manufacturer may provide paper format of the transaction records "to those licensed health care practitioner authorized to prescribe medication under state law or licensed individual under the supervision or direction of such a practitioner show dispenses product in the usual course of professional practice" (2013, sec. 582(b)(1)(C)(ii)).

In addition, by November 2017 a product identifier will be affixed or imprinted to each package and homogenous case of a product in a transaction entering the PSC {sec 582(b)(2)(A)}. Furthermore, the manufacturer will maintain the product identifier information for a period of six years after the transaction date {sec 582(b)(2)(A)}. The exception is where a package with a required SNI doesn't require a unique device identifier {sec 582(b)(2)(B)}.

Products that are returned are classified as saleable and nonsaleable. Saleable returns that the manufacturer plans to return to commerce will have verified the product identifier and SNI for each homogenous case or not a homogenous case on each package {sec 582(b)(4)(E)}. A manufacturer who is returning a nonsaleable returned product back to the

seller, such as manufacturer, wholesale distributor, repackager, or to a person acting on the behalf of such person which includes returns processor, will not have to include transaction records upon transfer {2013, sec 582(b)4(F)}.

3.5.2 Wholesale Distributor

The wholesale distributor (ADR and non-ADR) is not allowed to accept ownership of any product without the transaction records on or before taking ownership and from only an authorized trading partner by January 1, 2015 {sec. 582(c)(1)(A)}. The exception will be in the case where the product was purchased from a manufacturer, then only TS and TI is required. Additionally, six years after the enactment of the DSCSA in November 2019, the wholesale distributor will not be allowed to have product transactions without a product identifier {sec. 582(c)(2)}.

The wholesale distributor will provide to the buyer the standard transaction records of the product being shipped. If the wholesale distributor had purchased directly from the manufacturer, the TS will state that the wholesale distributor bought the products directly from the manufacturer {sec. 582 (c)(1)(A)(ii)(I)(aa)(AA)}. As like the manufacturer, the wholesale distributor will keep the transaction records for a period of six years {sec. 582 (c)(1)(A)(v)}.

The wholesale distributor by January 1, 2015 will have in place systems to allow for verification of suspect products or a verification requested by the Secretary for products that are in their possession or control {2013, sec 582(c)(4)}. The records of the investigation will be kept for a period of six years after the conclusion of the investigation {sec. 582 (c)(4)(A)(iii)}. An electronic database can be used to maintain the transaction records for verification purposes {sec. 582 (c)(4)(C)}.

3.5.3 Dispenser

By January 1, 2015, the dispenser will not accept any product without the transaction records {sec. 582(d)(1)(A)} and only from an authorized trading partner {sec. 582 (d)(3)}.

When the dispenser transfers the ownership of products to another trading partner (excluding patients and returns), the transaction records will be transferred on or before the shipment of product to the new owner. A dispenser is not allowed to accept any product from an authorized trading partner that does not have a product identifier encoded by November 2020. Dispensers can enter into an agreement with a third party (including a wholesale distributor) for the purpose of maintaining transaction records as required by the DSCSA except that the obligation and responsibility of the system is still with the dispenser.

In the case of saleable returns, the returned product may be sent back to the trading partner that sold them the product without having to produce the transaction records. In the case of the nonsaleable returns, a dispenser may return the product back to the manufacturer, the wholesale distributor, the repackager, a returns processor, or a person representing such a person without providing transaction records {2013, sec. 582(d)(1)(B)}.

By January 1, 2015, a dispenser is required to have systems in place for the purpose of verification of suspect products or to allow inquiries by the governmental and state agencies {sec. 582(1)(D) and 582(4)}. In the case of an investigation of {sec. 582(4)((A)(iv)} and disposition of {sec. 582(4)((A)(v)} a suspect product, all records of the investigation will be kept for a period of six years after the conclusion of the investigation. A secure electronic database can be used for the purpose of maintaining the transaction records for verifications and investigational records which can be maintained by the dispenser or a third party {2013, sec. 582(4)(C)}.

3.5.4 Repackager

A repackager as defined by {sec. 581(16)(A)} and by January 1, 2015 will not accept product from an unauthorized trading partner {sec. 582(e)(3)} without the transaction records. When the ownership of a product is being transferred from the repackager to another authorized trading partner, the repackager is responsible to transfer the transaction records to the new owner on or before the time of the transaction {sec. 582(e)(1)(A)(i, ii, iii)}. By November 2018, a repackager will affix or imprint a new product identifier to each package or homogenous case that will be introduced into the USPSC {sec. 582(e)(2)(A)(i)}. The repackager will maintain the information on the new product identifier for a period of six years after the date of the transaction {sec. 582(e)(2)(A)(ii)}. When the repackager breaks up a package that had an original manufacturer product identifier affixed or imprinted upon it, the repackager will maintain the association between the original manufacturer product identifier and the repackager product identifier for a period not less than six years {sec. 582(e)(2)(A)(iv)},

By January 1, 2015, repackager will have a system in place for the purpose of verification of suspect products that is in the repackager's control or possession or upon the request of verification from the Secretary which has determined the repackager is in control or in possession of suspect product {sec. 582(e)(4)(A)(i)}. Investigational records of a suspect product will be maintained for a period of six years after the investigation has concluded {sec. 582(e)(4)(A)(iii)}.

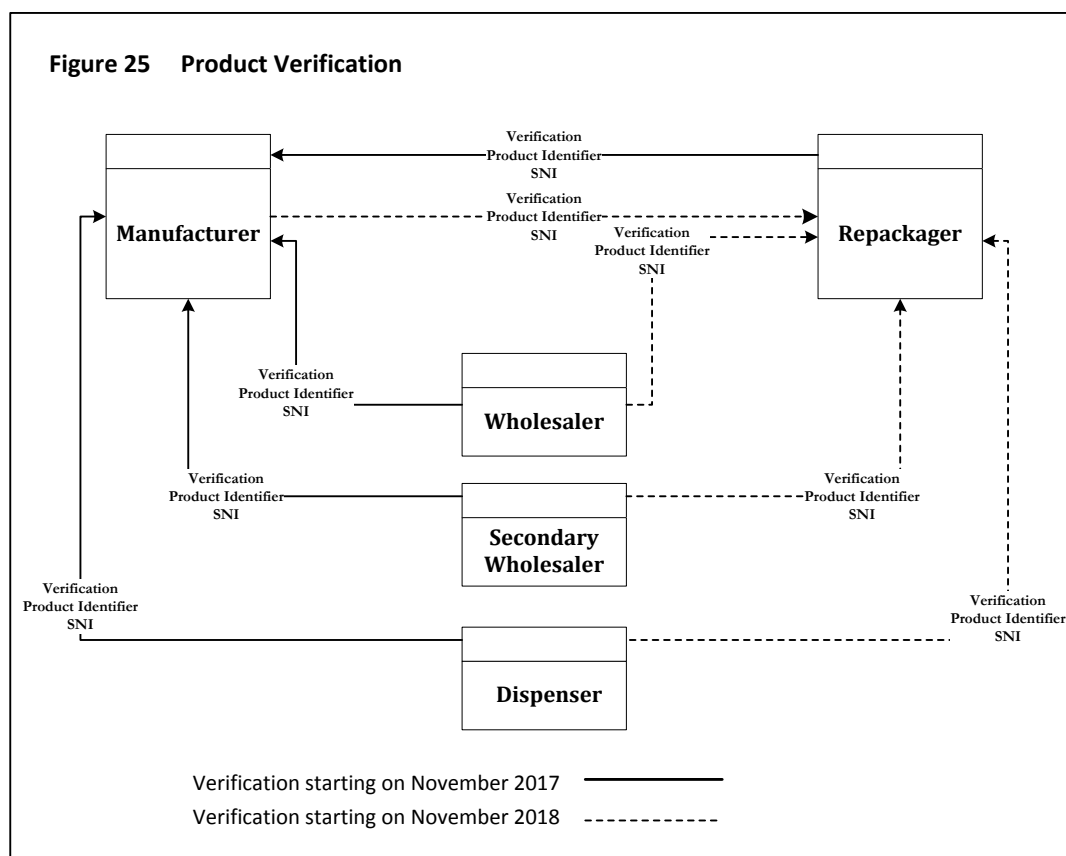
At the start of November 2018, a repackager receiving a request for verification of a product by the requesting trading partner by using the product identifier including the SNI will notify the requestor within 24 hours or a time period deemed reasonable by the Secretary whether the product identifier is valid. The verification requestor is required to be

in possession or control of the product in question. If the repackager deemed the product being verified to be illegitimate, the repackager will notify the requestor and start the investigation of a suspect product as described in {2013, sec. 582 (e)(4)(A)}.

3.6 Verification of Product Identifiers and SNI Requirements

Starting in November 2017, a manufacturer will process a verification request from an authorized repackager, wholesale distributor, or dispenser that is in control or possession of a product that it believes was created by the manufacturer. The manufacturer that receives the request will verify the product identifiers and SNI within 24 hours after receiving the request or a time period deemed reasonable by the Secretary to notify the requestor as to the status of product identifier and SNI. In the case where the product identifier does not correspond to the manufacturer's records of product identifiers, then the product is believed to be suspect and the requestor is notified as such {2013, sec 582(b)(2)(C)}. (see Figure 25)

Starting in November 2018, a repackager will process a verification request from an authorized manufacturer, wholesale distributor, or dispenser that is in control or possession of a product that it believes to be repackaged by the repackager. The repackager that receives the request will verify the product numbers and SNIs within 24 hours after receiving the request or a time period deemed reasonable by the Secretary to notify the requestor as to the status of product identifier and SNIs. In the case where the product identifier does not correspond to the repackager records of product identifiers, then the product is believed to be suspect and the requestor is notified as such. {2013, sec 582(e)(4)(C)} (see Figure 25)

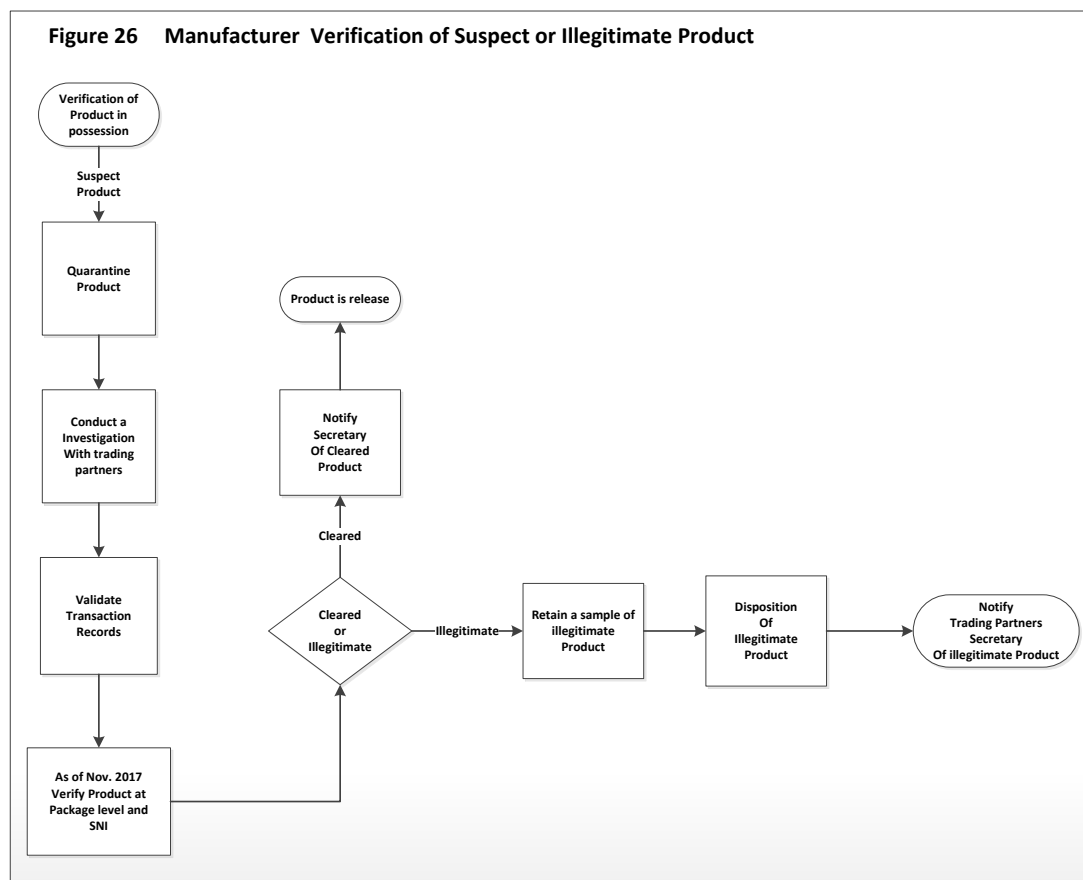


3.7 Suspect or Illegitimate Product Procedures Requirements

3.7.1 Manufacturer

Once the manufacturer has determined or has been notified by the Secretary that a suspect product is in their possession, the product is quarantined. An investigation is started with the manufacturer's trading partners to determine whether the product in question is illegitimate or not. The investigation steps are to validate the transaction records that are in the possession of the manufacturer of the suspect product. Starting in November 2017, the investigational steps will include the validation of product at the package level and SNI. If one of the results of the investigation is to clear the product in question, then the Secretary is notified of the product clearance and then the product is released to the market.

If the product in question is deemed to be illegitimate, a sample of the illegitimate product is taken for further physical examination or laboratory analysis by the manufacturer or the Secretary. The illegitimate product is disposed of in a manner appropriate to the manufacturer. The Secretary and all immediate trading partners are notified within 24 hours of determination of the product to be illegitimate. (see Figure 26)

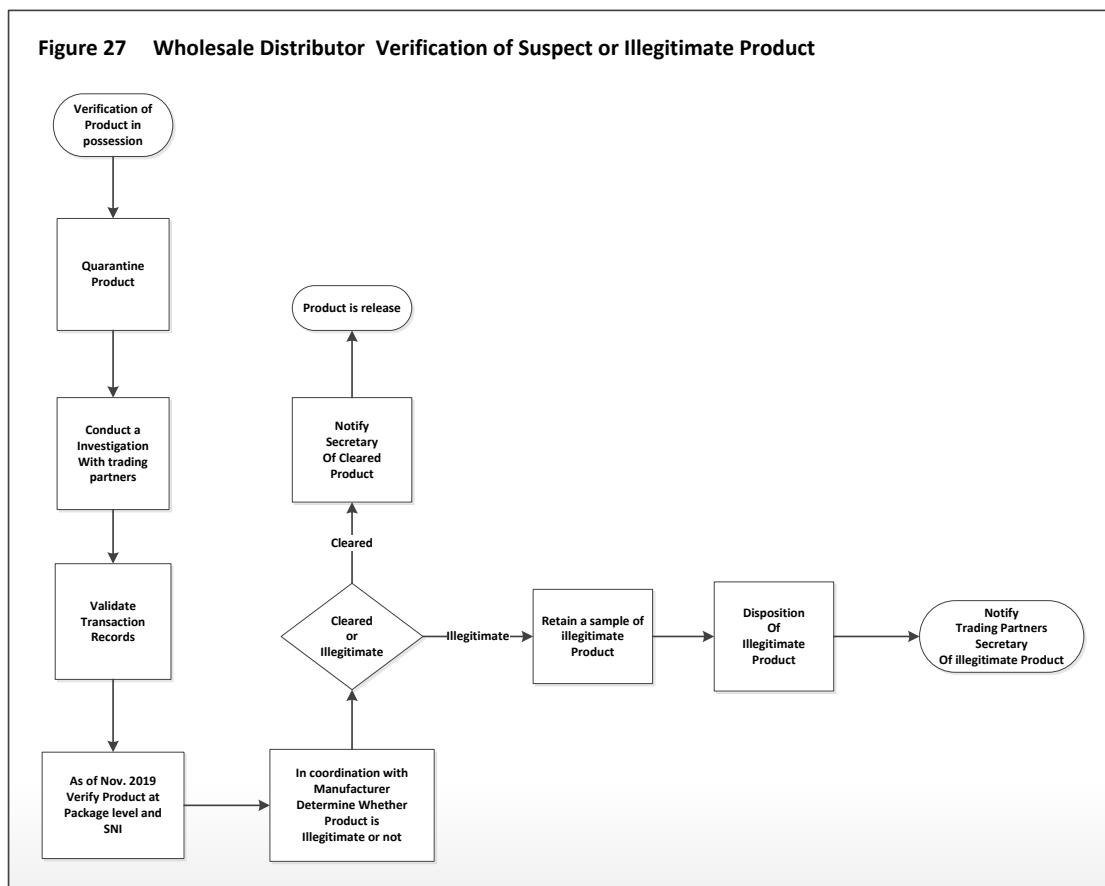


3.7.2 Wholesale Distributor

Once the wholesale distributor has determined or has been notified by the Secretary that a suspect product is in their possession, the product is quarantined. An investigation is started in coordination with the wholesale distributor's trading partners to determine whether the product in question is illegitimate or not. The investigation steps are to validate the transaction records that are in the possession of the wholesale distributor of the suspect

product. Starting in November 2019, the investigational steps will include the validation of product at the package level and SNI. If one of the results of the investigation is to clear the product in question, then the Secretary is notified of the product clearance and then the product is released to the market.

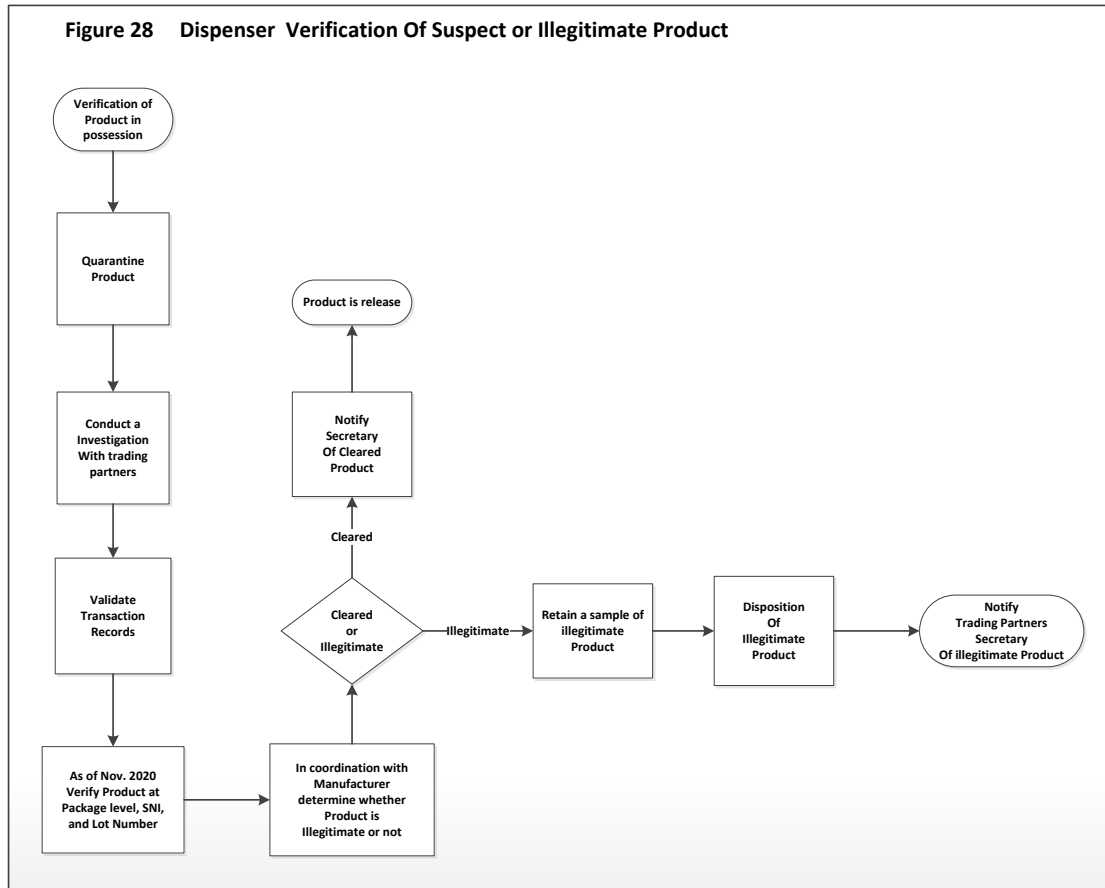
In coordination with the manufacturer, if the product in question is deemed to be illegitimate, a sample of the illegitimate product is taken for further physical examination or laboratory analysis by the manufacturer or the Secretary. The illegitimate product is disposed of in a manner appropriate to the wholesale distributor. The Secretary and all immediate trading partners are notified within 24 hours of determination of the product to be illegitimate. (see Figure 27)



3.7.3 Dispenser

Once the dispenser has determined or has been notified by the Secretary that a suspect product is in their possession, the product is quarantined. An investigation is started with the dispenser's trading partners to determine whether the product in question is illegitimate or not. The investigation steps are to validate the transaction records that are in the possession of the dispenser of the suspect product. Starting in November 2020, the investigational steps will include the validation of product at the package level, SNI, and lot number. If one of the results of the investigation is to clear the product in question, then the Secretary is notified of the product clearance and then the product is released to the market.

In coordination with the manufacturer, if the product in question is deemed to be illegitimate, a sample of the illegitimate product is taken for further physical examination or laboratory analysis by the manufacturer or the Secretary. The illegitimate product is disposed of in a matter appropriate to the dispenser. The Secretary and all immediate trading partners are notified within 24 hours of determination of the product to be illegitimate. (see Figure 28)



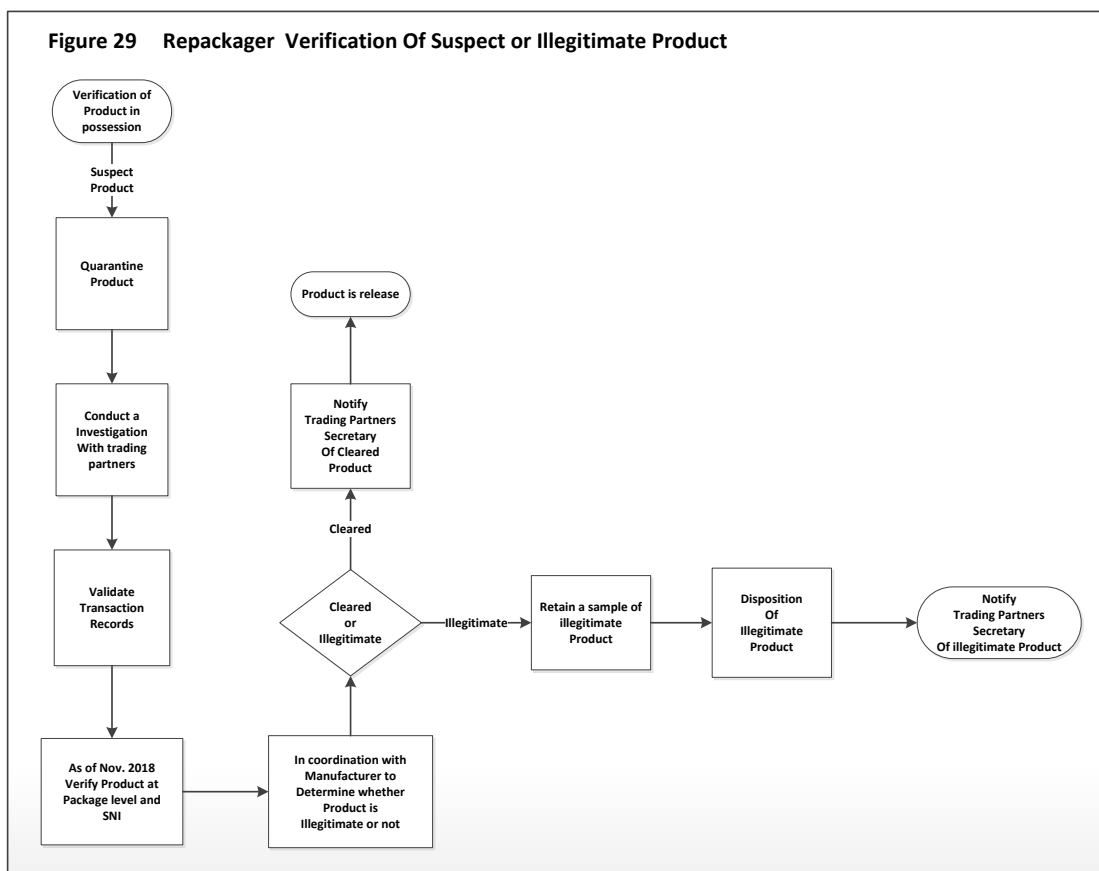
3.7.4 Repackager

Once the repackager has determined or has been notified by the Secretary that a suspect product is in their possession, the product is quarantined. An investigation is started with the repackager's trading partners to determine whether the product in question is illegitimate or not. The investigation steps are to validate the transaction records that are in the possession of the repackager of the suspect product. Starting in November 2018, the investigational steps will include the validation of product at the package level and SNI. If one of the results of the investigation is to clear the product in question, then the Secretary is notified of the product clearance and then the product is released to the market.

In coordination with the manufacturer, if the product in question is deemed to be illegitimate, a sample of the illegitimate product is taken for further physical examination or

laboratory analysis by the manufacturer or the Secretary. The illegitimate product is disposed of in a manner appropriate to the repackager. The Secretary and all immediate trading partners are notified within 24 hours of determination of the product to be illegitimate. (see Figure 29)

All trading partners' investigational records will be kept for a period of six years at the conclusion of the investigation.



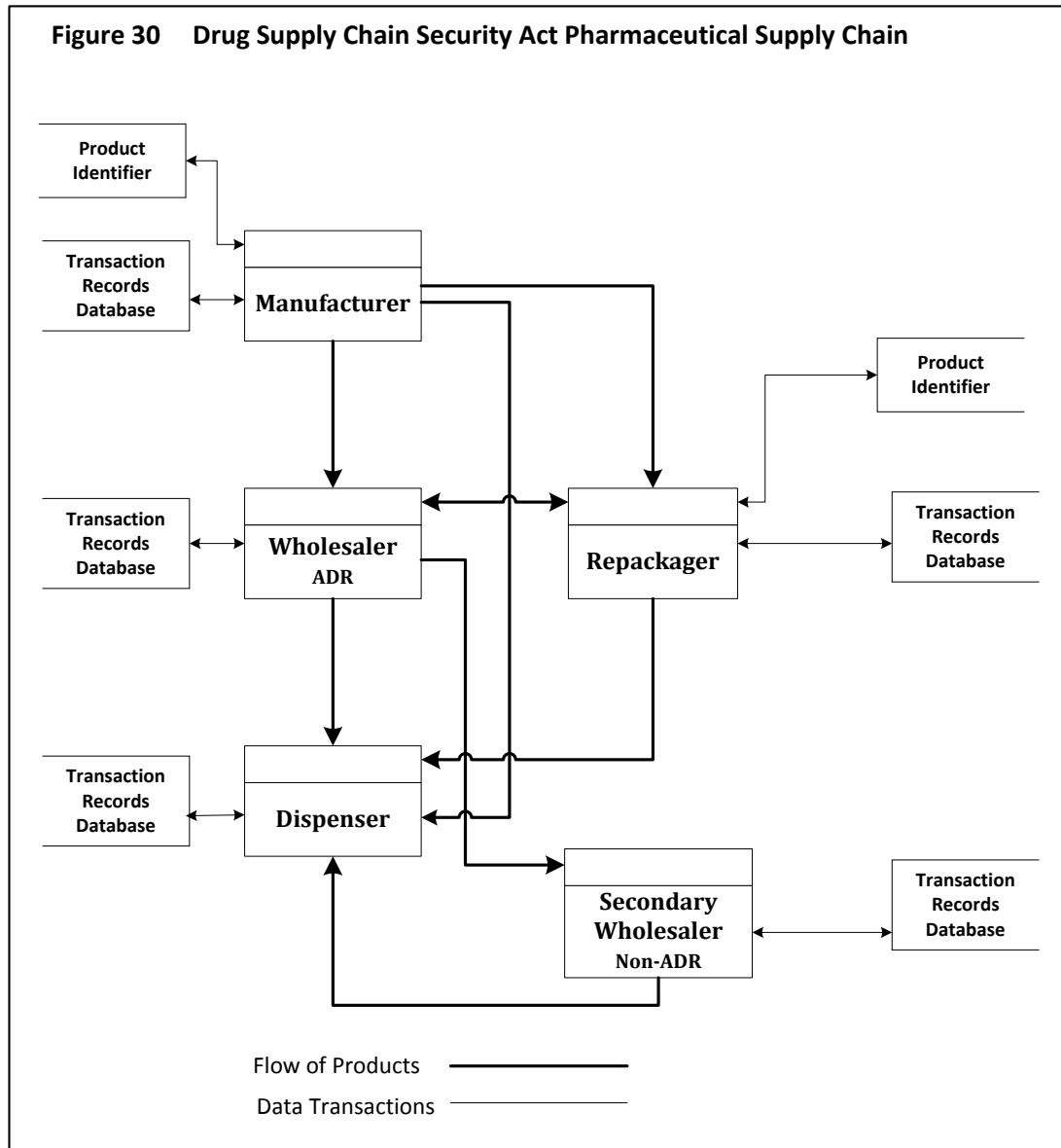
3.8 Electronic Database

All of the trading partners of the USPSC, excluding 3PLs, are required to have systems in place by January 1, 2015 to maintain transaction records for a period of six years and investigational records for a period of six years after the investigation has concluded.

According to the DSCSA, an electronic database can be used to maintain these records and can be developed and maintained by the trading partners or by a third part vendors.

Although a third party can maintain and operate a database, it is still the responsibility of each trading partner to ensure the capability of its database to be able to satisfy a request for verification.

What might this database look like? Well, DSCSA does stipulate what the TS, TI, and TH contains. TS is a document containing required language and TI must contain certain fields. Additional information would be the product identifiers that must be maintained by the manufacturer and the repackager for verification and for a period of six years. Furthermore, the repackager must maintain the relationship between the manufacturer product identifier and the new product identifier that the repackager has attached to the package and homogenous case as required. The transaction history records will include all the TS and TI transactions that have occurred before arriving at its current location in the USPSC. From this information, the transaction history would be a series of TI and TS associated with each transaction. The following is a possible logical model Entity-Relationship diagram (ERD) design for the DSCSA schema. All ERDs were created using Microsoft Visio 2010. (see Figure 30)

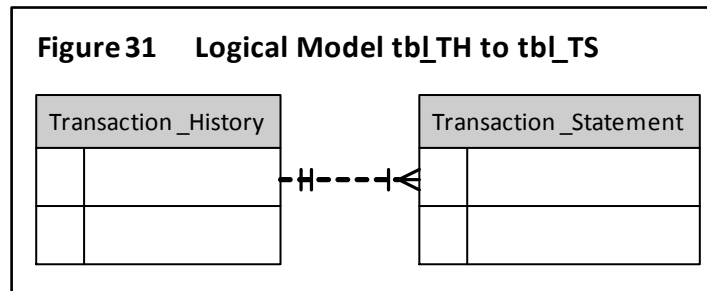


3.8.1 Manufacturer Logical Model ERD

The manufacturer logical model ERD would contain the Transaction History table (tbl_TH), Transaction Statement table (tbl_TS), and Transaction Information table (tbl_TI). Tbl_TH tracks the old TS and TI information going back to the manufacturer if applicable and the current TI and TS associated with the current transaction.

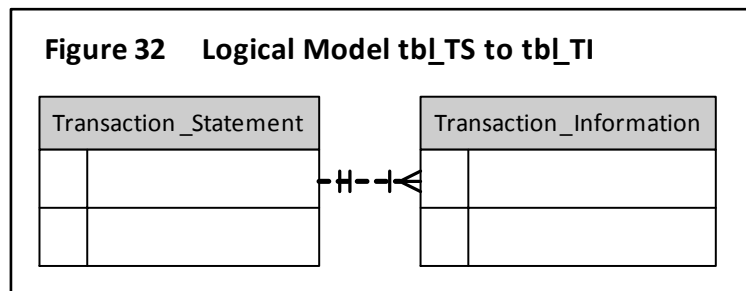
Minimum cardinality for each instance in the tbl_TH would be at least one instance in the tbl_TS. Maximum cardinality would be one instance in the tbl_TH would relate to

many instances in the tbl_TS. The logical model ERD design between tbl_TH and tbl_TS would be the following: (see Figure 31)



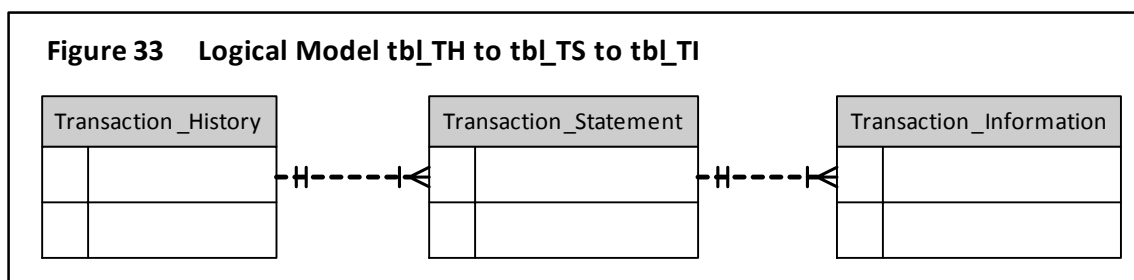
The reverse of the relationship would be one or more instances in the tbl_TS would relate to one instance in the tbl_TH.

A single transaction would contain one tbl_TS instance for the shipment and one or more TIs to reflect the contents of the shipment. The minimal cardinality would be one instance in the tbl_TS that would relate to one instance in the tbl_TI. The maximum cardinality between tbl_TS and tbl_TI would be one instance in the tbl_TS that would relate to many instances in the tbl_TI. The logical model ERD would look like Figure 32:



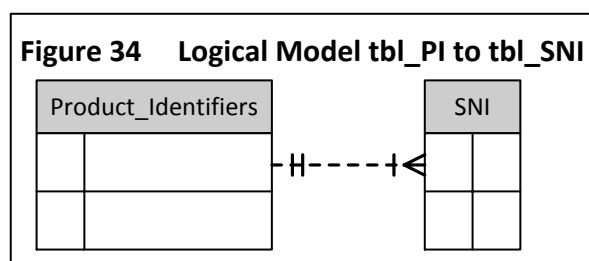
In reverse, one or more instances in tbl_TI would relate to one instance in the tbl_TS.

By combining the two logical ERDs (Figure 31 and Figure 32), the resultant would be the relationship between tbl_TH, tbl_TS, and tbl_TI. (see Figure 33)



After November of 2017, the manufacturer is required to affix or imprint a product identifier to each package and homogenous case of a product and maintain the records of these product identifiers. The product identifier includes standardized numerical identifier (SNI), lot number, and expiration date of the product. Since the SNI contains the package NDC number, the name of the drug and package information is acquired from it.

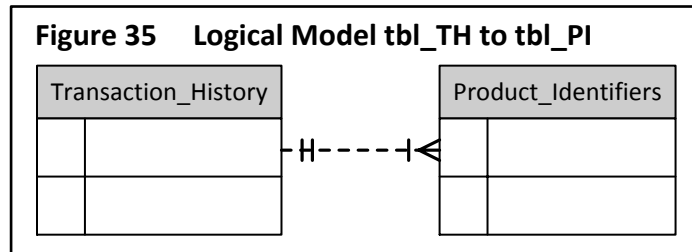
The minimum cardinality of a product identifier table (tbl_PI) would be one instance of the product identifier that would relate to one instance of SNI table (tbl_SNI). The maximum cardinality would be one instance of a product identifier that would relate to one or more instances of SNI. (see Figure 34)



In reverse, one or more instances in tbl_SNI would relate to one instance in the tbl_PI.

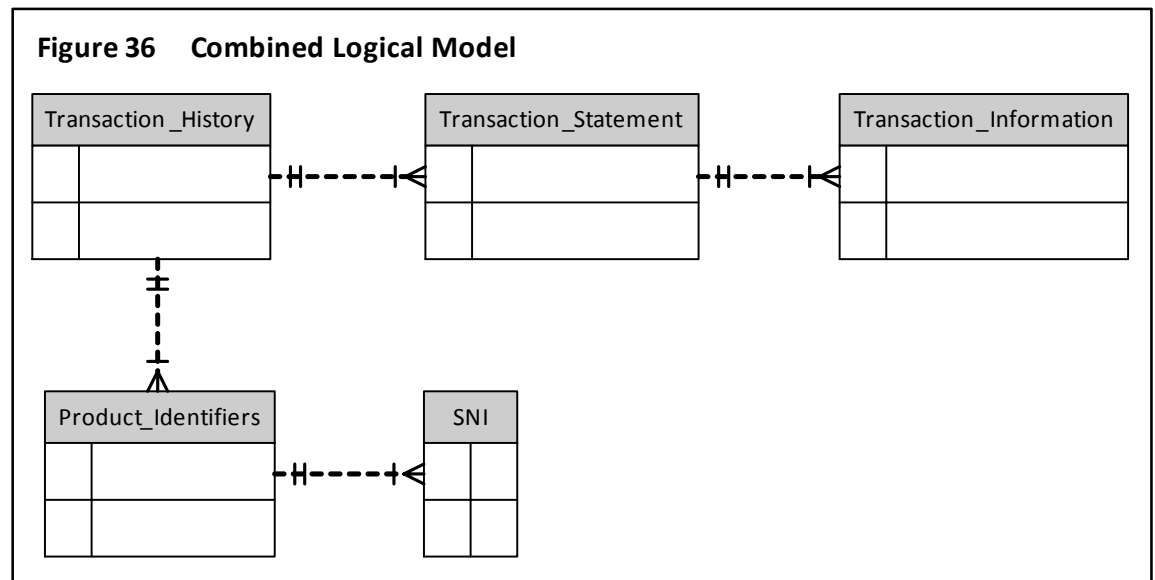
For example a non-homogenous case of product could contain multiple packages each with their own SNI, lot number, and expiration date. Another example would be a homogenous case of product that would relate to a different SNI with the same lot number and expiration date.

Although it is not required by DSCSA, we will tie the transaction history, statement, and information to the product identifiers. The minimal cardinality would be for a single instance in the tbl_TH to refer to at least one instance of product identifier. The maximum cardinality would be for one instance in the tbl_TH there would be many instances in the tbl_PI. The logical model ERD would look like the following: (see Figure 35)



In reverse, one or more instances in tbl_PI would relate to one instance in the tbl_TH.

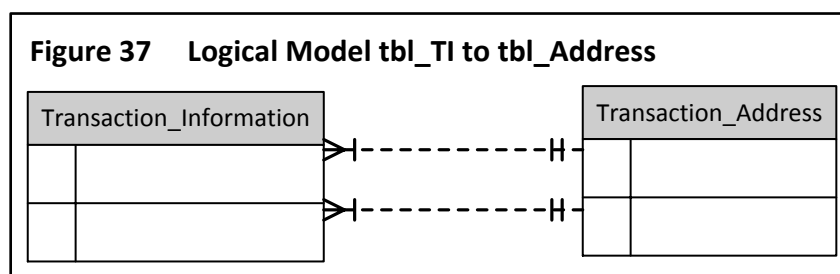
Let us combine all the manufacturer logical model ERDs together and they would look like Figure 36:



In the tbl_TI, there is a requirement of the senders and receiver information.

Normally, you would probably have done business with the sender or receiver multiple

times. So, the business name, address, contact person information would be used over and over again for each transaction associated with them. This implies that one entry in the Transaction Address (tbl_Address) table could be mapped to multiple entries in the tbl_TI for sender and receiver. (see Figure 37)



The tbl_TI is required to have several columns such as product name, strength, dosage, package NDC, container size, number of containers, lot number, transaction date, shipping date, sender information, and receiver information. The tbl_Address would have the following columns: business name, street address, city, state, postal code, country, contact name, contact title, contact phone number, contact email, contact URL, address identification, license number, license state, and license agency. Most of the columns are self explanatory except for address identification which could be the plant number, GS1 Global Location Number (GLN), and any other means to identify the address. (see Figure 38)

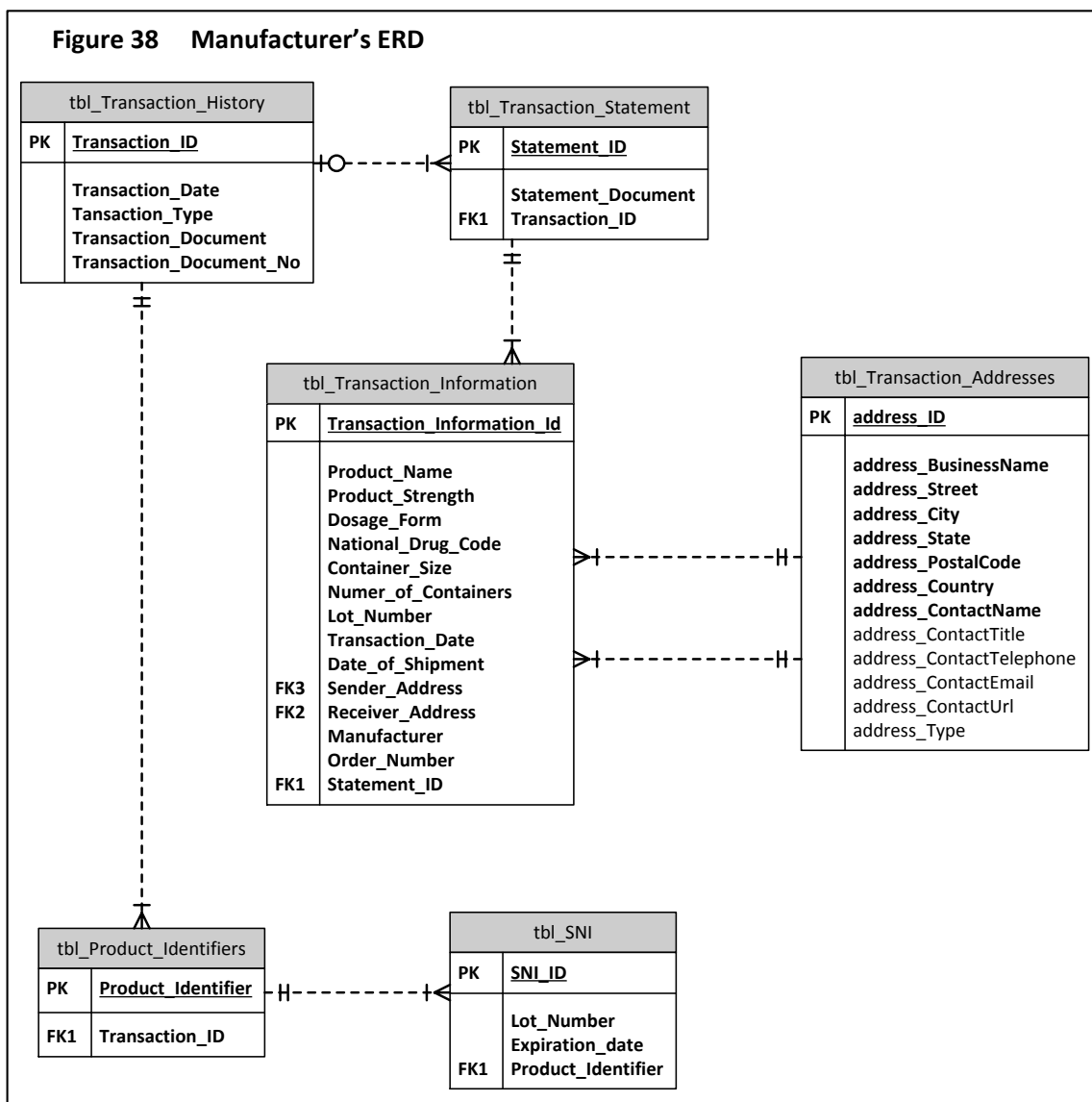
Each entry in the tbl_TH would map to at least one or more product identifiers. It is not required to maintain a relationship between the tbl_TH and the tbl_PI. However, it would be nice for verification purposes to be able to track what product identifiers are related to a particular transaction record. (see Figure 38)

Each product identifier is mapped to one lot number, expiration date, and standard numerical identifier (SNI) for each package and/or homogenous case. In the situation of a homogenous case, one product identifier could be attached to the case with multiple packages, each affixed or imprinted onto each package a SNI. This would create a

relationship of one product identifier to one or more SNIs. This implies that the product identifier table entry would be mapped to one or more entries in the SNI table. (see Figure 38)

The tbl_TH would have a primary key which would be a sequence number and we will call it Transaction_ID. The other column in this table could be Transaction_Date. Another column might be the Transaction_Document with values such as "invoice", "purchase order", "shipping number", or "return authorization number". Another column could be Transaction_Document_No which would be the document number such as the invoice number or purchase order which is related to Transaction_Document. Another column that might be needed is the Transaction_Type which would have values of "sale", "return", "transfer", or others. (see Figure 38)

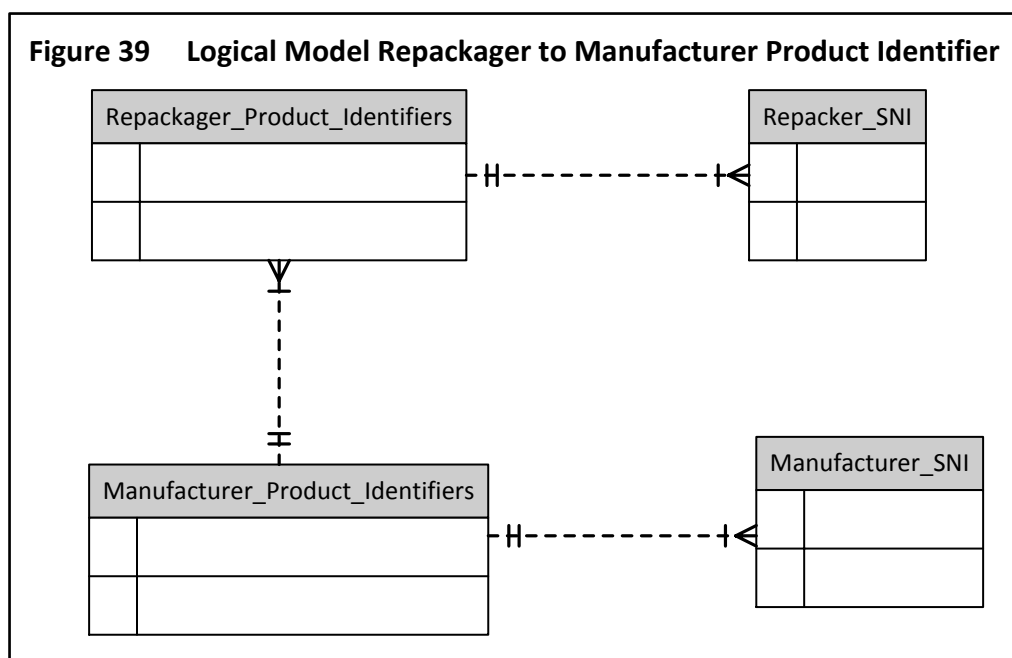
The tbl_TS would have a primary key called Statement_ID. The other column would be the Statement_Document. The statement document could be a scanned, text type, or electronically formatted document. (see Figure 38)



3.8.2 Repackager ERD

The repackager logical model ERD would be the same as the Manufacturer logical model ERD except for the additional tables required for mapping the repackager new product identifiers to the original manufacturer product identifiers. The repackager logical model ERD would have the same tbl_TH, tbl_TS, tbl_TI, tbl_PI, and tbl_SNI tables and relationships as the manufacturer's logical model ERD. However, the two new tables would contain the manufacturer product identifier and associated SNIs. (see Figure 39)

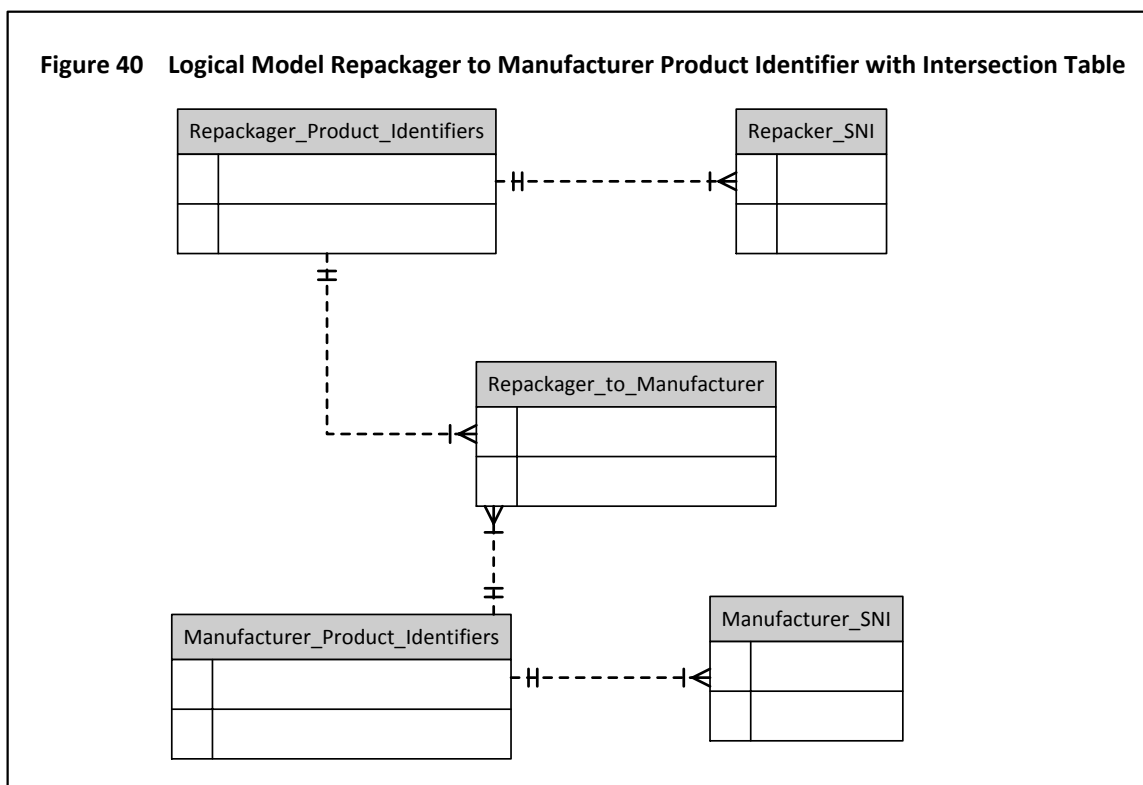
The additional tables in the repackager logical model ERD have to do with the DSCSA requirement. Repackagers must maintain records for a period of six years when they attach a new product identifier to a product that had a manufacturer product identifier attached to it. Repackagers have to show the relationship between the new repackager product identifier to that of the manufacturer product identifier. An example of this relationship would be the following: (see Figure 39)



For example, if the repackager splits the manufacturer case into two cases of equal quantity, then the manufacturer product identifier attached to the manufacturer case would have to be mapped to the two new repackager product identifiers. The repackager would have to keep a record of the remapped manufacturer product identifier to the two new repackager product identifiers for a period of six years.

The above example explains the need for a foreign key in the repackager product identifier table to satisfy the requirement of mapping one manufacturer identifier to one or more repackager product identifiers. The cardinality between the manufacturer product

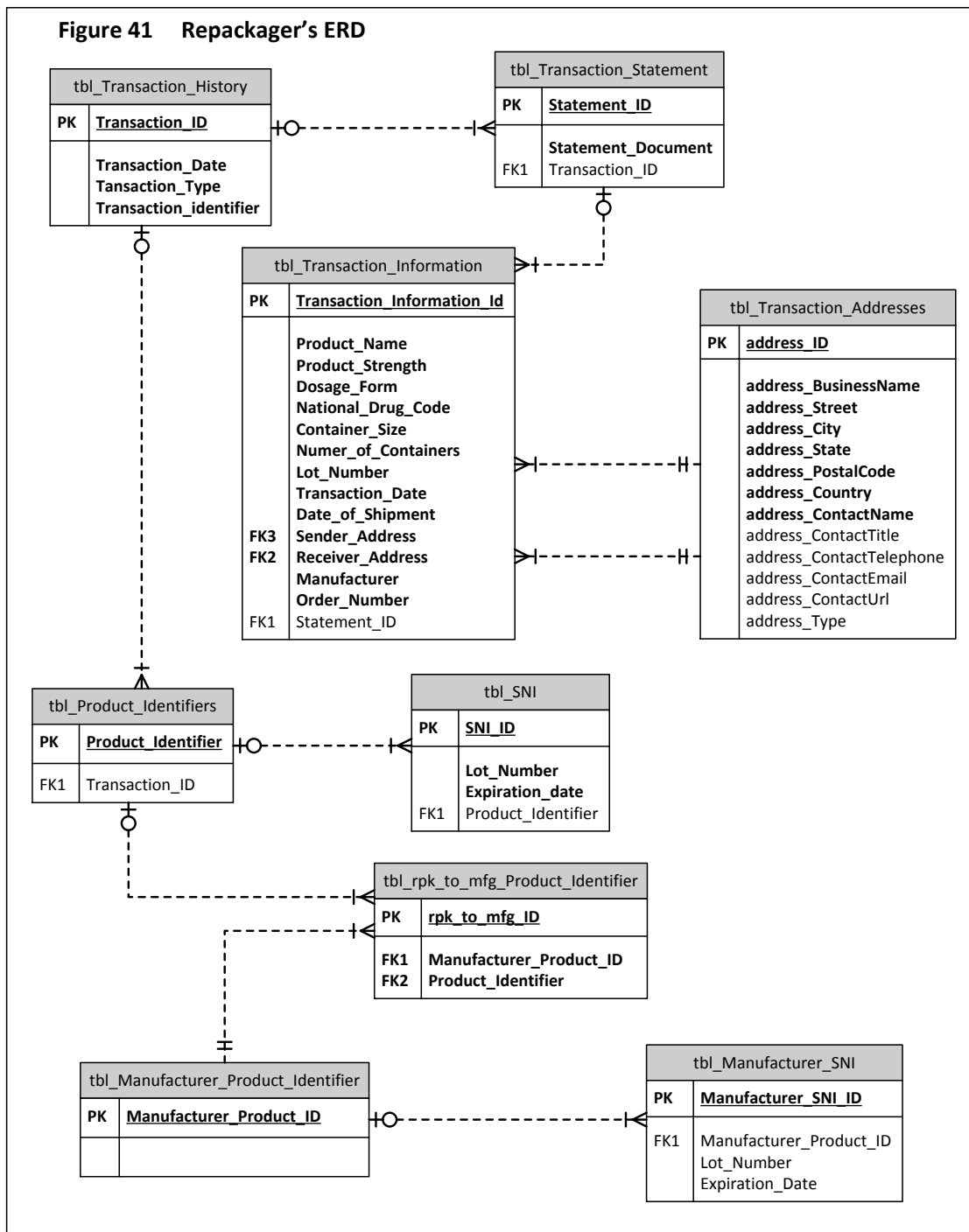
identifier table to the repackager product identifier would be one to many. In the case where the repackager were to consolidate the number of manufacturer cases to a single box for instance, then the relationship would be one repackager product identifier to many manufacturer product identifiers. Since both examples could exist, an intersection table would be required. Now the relationship between repackager product identifier to manufacturer identifier would be many to many. The above described relationship would look like the following: (see Figure 40)



The SNIs would be found in both manufacturer and repackager SNI tables and may be redundant but would help in the remapping of SNIs to repackager product identifiers as the repackager SNI table would have to contain the same SNIs in the manufacturer SNI table.

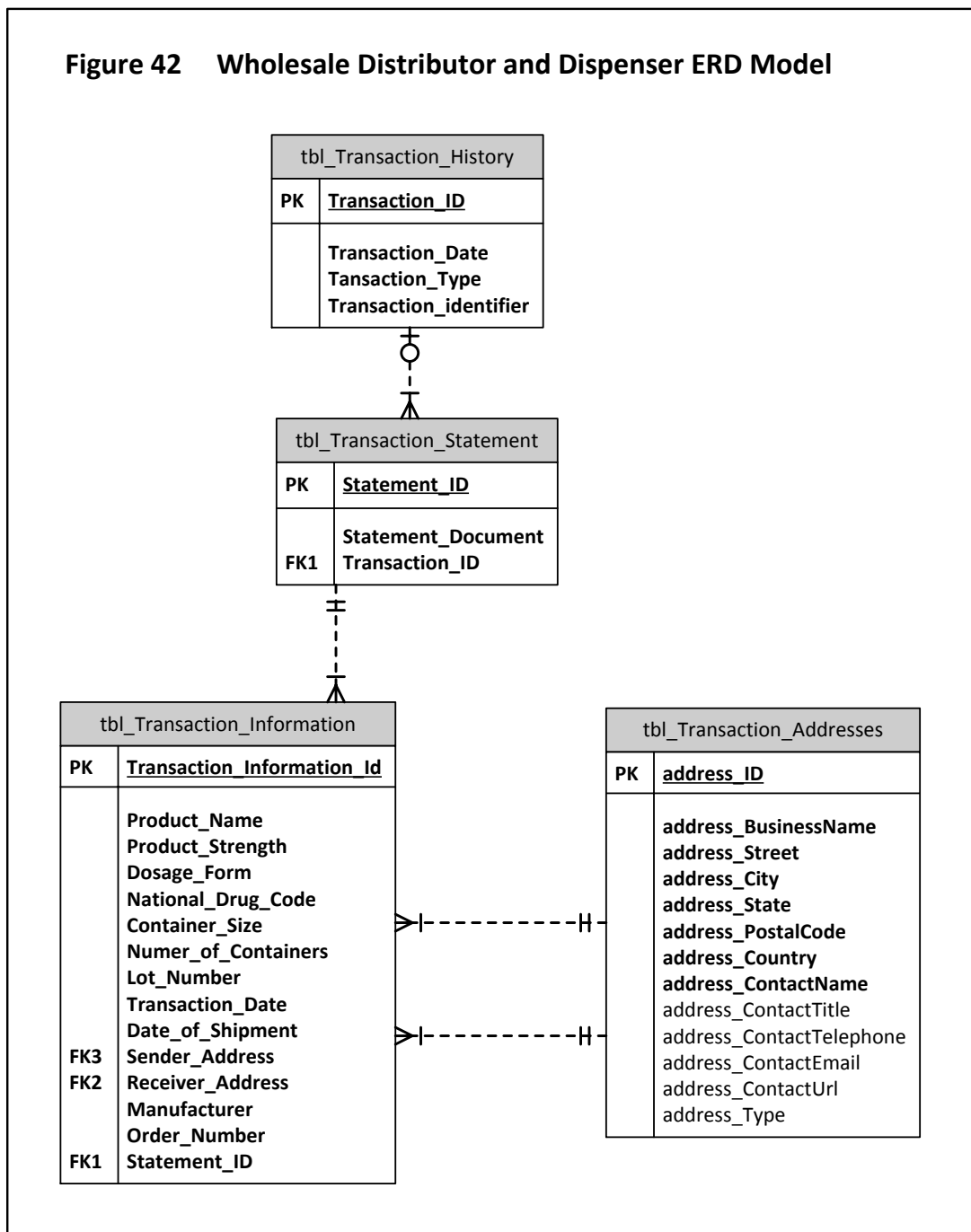
The logical model ERD for the repackager would be the following: (see Figure 41)

Figure 41 Repackager's ERD



3.8.3 Wholesale Distributor and Dispenser

The wholesale distributor and dispenser logical model ERD would be the same because their responsibility would be to maintain the transaction records only. The logical model ERD would look like the following: (see Figure 42)



3.9 Product Identifier Verification Implementation

3.9.1 Introduction

On November 27, 2014, the FDA will produce a draft guidance document that creates standards for the transaction records being exchanged between trading partners in paper or electronic format. However, at this time there will not be any guidance documents to cover verification procedures that will be performed between trading partners. The only requirement is to create a system to allow verification by trading partners by January 1, 2015. The product identifier is used to verify that the product came from the manufacturer or repackager. We know from the DSCSA document that a product identifier will be a

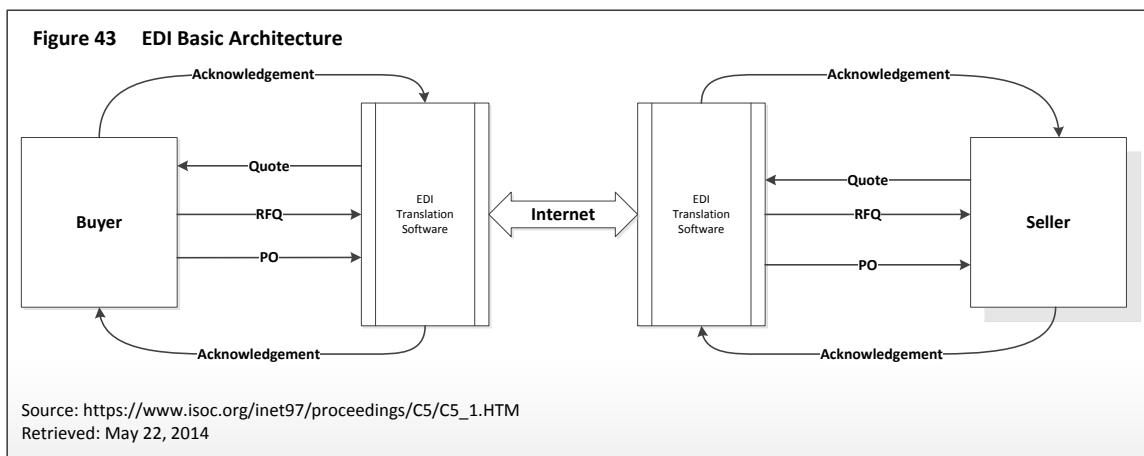
standardized graphic that includes, in both human readable form and on a machine readable data carrier that conforms to the standards developed by a widely recognized international standards development organization, the standardized numerical identifier, lot number, and expiration date of the product. (2013, sec. 581(14))

There are two internationally accepted standards: Electronic Data Interchange (EDI) and GS1 Global Data Synchronization Network (GDSN).

3.9.2 Electronic Data Interchange (EDI)

EDI is business-to-business (B2B) software that has been widely available since the 1980s (Lim & Palvia, 2001) and developed under two main standards: American National Standards Institute (ANSI) X12 and United Nations/Electronic Data Interchange for Administration, Commerce, and Transport (UN/EDIFACT) (Kabak & Dogac, 2010). EDI is a paperless system that uses computers for the exchange of business documents such as an invoice and a purchase order (PO) between a buyer and a seller using a standard format via

the Internet (Copeland, 1997; Kabak & Dogac, 2010; Lim & Palvia, 2001). The buyer creates an RFQ on their computer and EDI creates an electronic version of the RFQ and sends it to the seller's computer system. The seller order entry system receives the PO electronically via their EDI software and processes it by updating their computer system and then sends an acknowledgement back to the buyer. The seller sends a quote back to the buyer and an acknowledgement is sent back to the seller of receipt. Then the buyer sends a PO to the seller and an acknowledgement is sent back. In addition, inventory replenishment systems and electronic funds transfers (ETFs) are part of EDI. The following is an example a basic EDI architecture (Copeland, 1997). (see Figure 43)



3.9.3 GS1 US

GS1 US is a not-for-profit organization that supplies the world's most accepted supply chain standards (GS1, Unknown). These standards include globally unique numbering formats for identifying supply chain objects using barcodes and radio frequency identification tags (RFID)(GS1, Unknown). These standards are used for the storage of the identification numbers and data sharing. The main purpose of GS1 US is to organize industrial communities to solve supply chain problems via the GS1 standards.

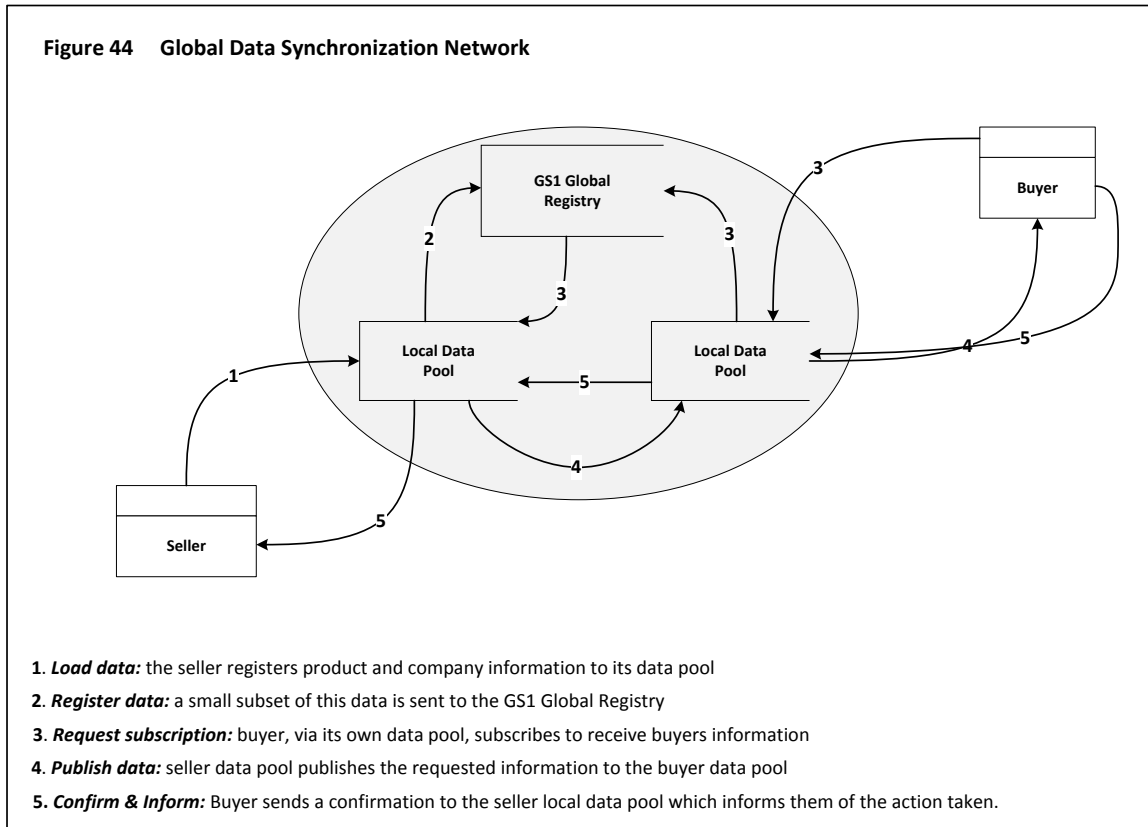
Due to the FDA Amendments Act (FDAAA) of 2007 and FDA Safety and Innovation Act (FDASIA) of 2012 which directed the FDA to create unique device identification system for medical devices, GS1 became one of the accredited agencies for unique device identifiers (UDIs). UDIs will be created and maintained by device labelers according to global device identification standards maintained by the FDA-accredited issuing agencies. The FDA will maintain and operate the Global Unique Device Identification database (GUDID) for all UDI labeled devices. GDSN is the system used to populate the FDA GUDID. (MedTech, 2013)

3.9.4 GS1 GDSN

GS1 GDSN is a real time system that allows sellers and buyers to access and exchange product information (GS1, Unknownc). In our case, buyers and sellers are the trading partners as defined by the DSCSA. For the manufacturers to share product information via product identifiers, they are required to insert their data into the data pool. The data pool is a database of GS1 standardized product information that is use to maintain and operate as a data exchange between trading partners as part of the GDSN.

The main purpose of GDSN is to store product data. GDSN can store up to 150 different attributes of a product such as those contained in 1-D and 2-D matrix barcodes (GS1, Unknownb). Another purpose is to provide shared data access and timely notification of additions, deletions, and modification of product information to the trading partners. GDSN provides globally defined standards along with a common set of rules and definitions that are applied to data representation and database access. The network part of GDSN consists of a number of central databases (data pools). The GS1 Global Registry is the GDSN data pool that contains a list of registered users, users' access rights to product information, and a data dictionary. The other data pools are master databases that contain

the subscribers' shared information. GDSN is monitored and maintained by the GS1 Member Organization but is operated by a third party solution provider, or other independent authority (GS1, Unknownb). The following is a diagram of GDSN (GS1, Unknownc). (see Figure 44)



Source: <http://www.gs1.org/gdsn/how>
Retrieved: July 4, 2014

3.9.5 EDI vs. GDSN for Product Verification

EDI is used for B2B transactions for inventory, invoice, and payment purposes.

GDSN is used for sharing product information between trading partners. Since we are going to verify product identifiers, GDSN is the better solution.

3.9.6 GTIN

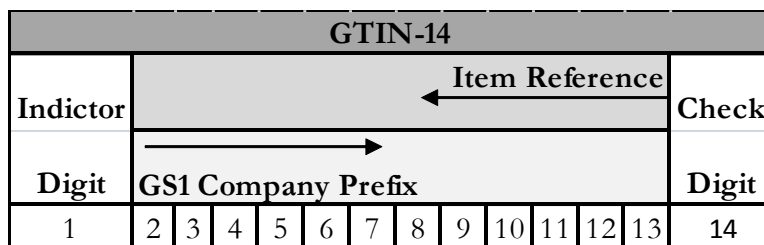
GS1 Global Trade Item Number (GTIN) is a unique number that identifies trade items throughout a supply chain (GS1, 2013d). A trade item can be a single item or a package configuration (case, carton, pallet). In addition, GTIN is a required component in GDSN. This requires the GTIN data in the barcode to be the same as the data stored in the GDSN databases. Thus, the GTIN value must be unique throughout the world.

For the GTIN to be unique, each company using GDSN must buy a subscription to the GDSN services. After obtaining a subscription from the GS1 GDSN service, a company is given a company prefix which consist of a GS1 Prefix and Company number (GS1, 2013b). The company prefix consists of seven to eleven digits that are part of the GTIN data structure. A digit has a value of 0 through 9. The GTIN structure begins with a indicator digit followed by a company prefix, item reference number, and the check digit. A GTIN can be 8, 12, 13, or 14 digits long. The following is a breakdown of the GTIN structure (GS1, 2013d). (see Figure 45)

Figure 45 GTIN Structure 8-14	
GTIN Digits	
Type	1 2 3 4 5 6 7 8 9 10 11 12 13 14
GTIN-8	0 0 0 0 0 0 N N N N N N N C
GTIN-12	0 0 0 0 0 0 N N N N N N N C
GTIN-13	0 N N N N N N N N N N N N C
GTIN-14	N N N N N N N N N N N N N C

Note: 0 - zero filled, N - digit, C - Check digit
Source: [http://www.gs1us.org/Portals/0/gs1 us library/standards/gs1 identification numbers/An Introduction to the Global Trade Item Number \(GTIN\).pdf](http://www.gs1us.org/Portals/0/gs1%20us%20library/standards/gs1%20identification%20numbers/An%20Introduction%20to%20the%20Global%20Trade%20Item%20Number%20(GTIN).pdf)
Retrieved: July 4, 2014

The digits between 2 and 13 (12 digits) are where the company prefix and item reference number is stored. The following is an example (GS1, 2013b). (see Figure 46)

Figure 46 Structure of a GTIN-14

Note: Item Reference number begins at digit 13 and grows to the left

GS1 Company Prefix number begins at digit 2 and grows to the right

Source: http://www.gs1.org/docs/gsmg/healthcare/GS1_Healthcare_GTIN_Allocation_Rules.pdf

Retrieved: July 4, 2014

The larger the company prefix, the smaller number of products that can be identified. The following figure gives a breakdown (GS1, 2014). (see Figure 47)

Figure 47 The GS1 Company Prefix

GS1 Company Prefix Size	Example	Number of Product that can be identified
Seven Digits	0NNNNNNN	100,000
Eight Digits	0NNNNNNNN	10,000
Nine Digits	0NNNNNNNNN	1,000
Ten Digits	0NNNNNNNNNN	100
Eleven Digits	0NNNNNNNNNNN	10

Source: <http://www.gs1us.org/resources/standards/company-prefix>

Retrieved: July 4, 2014

GTIN-14 could not be used to track National Package Drug Code which is ten digits in length and over 150,000 items as of May 19, 2014. Because there are a little over 78,000 drug products in the product NDC data with over 7,000 labelers, a drug manufacturer or repackager could choose a seven-digit company prefix and would be able to identifier up 100,000 products using their own product identifier value. A manufacturer or repackager

could choose an eight-digit company prefix and would be able to track up to 10,000 products. However, as a product identifier (GTIN-14) would have to exist for a period six years before being retired, a larger number for product identifiers may be required.

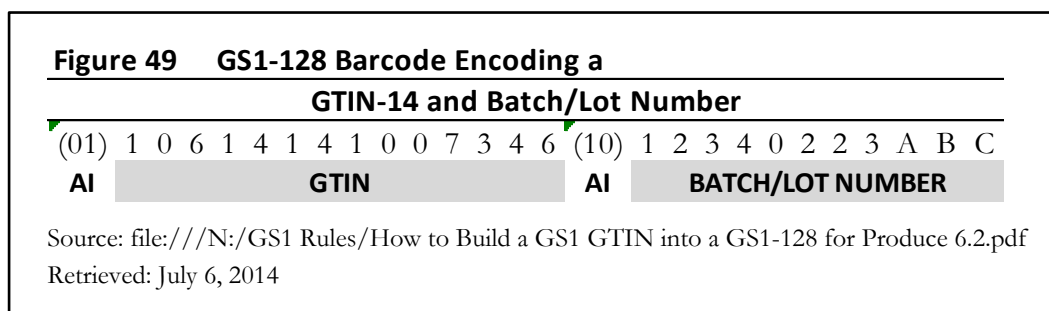
3.9.7 Product Identifier (GTIN-14)

Once the company has subscribed to GDSN and received their company prefix, the company will have the ability to create product identifiers (GTINs) and access the GS1 standards. The product identifiers along with serial number, batch/lot number, and expiration date can be stored in the GDSN and displayed at the item and the package level via 1-D and 2-D barcodes which is a requirement of DSCSA sec. 582(a)(9). A 2-D data matrix will be affixed to the package and 1-D or 2-D data matrix barcodes on the homogenous case {2013, sec. 582(a)(9)(A)(i-ii)}.

The 1-D barcode can be the GS1-128 that incorporates the product identifier into the barcode along with serial number, batch/lot number, and expiration date. GS1-128 has a 48 alphanumeric capacity that uses application identifiers (AI), uses unique GS1 identifiers, and is not omnidirectional. The following is an example of GS1-128 barcode that uses GTIN-14 with barcode values only (GS1, 2013c). (see Figure 48)

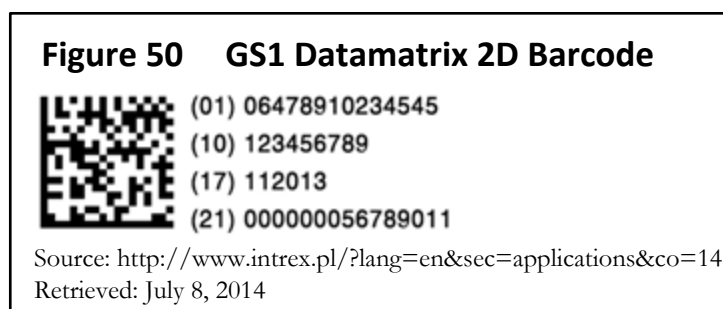
Figure 48 GS1-128 Barcode	
Encoding a GTIN-14	
(01)	1 0 6 1 4 1 4 1 0 0 7 3 4 6
AI	GTIN
Source: file:///N:/GS1 Rules/How to Build a GS1 GTIN into a GS1-128 for Produce 6.2.pdf	
Retrieved: July 6, 2014	

Next is an example of a GS1-128 barcode that includes the GTIN-14 and batch/log number (GS1, 2013c). (see Figure 49)



The value of (01) and (10) are application identifiers with (01) GTIN and (10) being batch/lot number. Remember GTIN-14 is our product identifier.

The 2-D data matrix barcode will be the GS1 DataMatrix (version ECC 200). GS1 DataMatrix has the capacity of 3116 numeric or 2335 alphanumeric, carries application identifiers, has a unique GS1 identifier, and is scanned by a camera-based device only (GS1, 2011). The following is an example of a GS1 Datamatrix. (see Figure 50)



This example has stored the product identifier (01), batch number (10), expiration date (17), and the serial number (21). This serial number could be the serial number required for the SNI. However, we haven't discussed how to incorporate the FDA NDC into GS1 standards.

FDA NDC is comprised of a ten-digits code that has different formats: 4-4-2, 5-3-2, and 5-4-1 (FDA, 2012c). The first segment is the labeler code which identifies the labeler. The second segment is the product code which denotes specific strength, dosage form, and formulation for a particular manufacturer. The third segment is the package code which

denotes package size and type. Package type can be package, box, carton, case, pouch, blister packs, or other containers listed in the NDC package table.

The following is an excerpt from the FDA labeler table retrieved from the FDA website on May 21, 2014. (see Figure 51)

Figure 51 NDC/NHRIC Labeler Codes

NDC Labeler Code	Firm Name
0002	Eli Lilly and Company
0003	E.R. Squibb & Sons, L.L.C.
0004	Genentech, Inc.
0005	Wyeth Pharmaceutical Division of Wyeth Holdings Corporation, a subsidiary of Pfizer Inc.
0006	Merck Sharp & Dohme Corp.
0007	GlaxoSmithKline LLC
0008	Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc.
0009	Pharmacia and Upjohn Company
0010	Boehringer Ingelheim Vetmedica, Inc.

Source: <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm191017.htm>
Retrieved: May 20, 2014

These labeler codes can be incorporated into the company prefix provided by GS1 (GS1, 2013a). For example, (see Figure 52)

Figure 52 GS1 Company Prefix using Labeler Code

GS1 Prefix	03
FDA NDC Labeler Code	0005
GS1 Company Prefix	030005

Source: http://www.gs1us.org/DesktopModules/Bring2mind/DMX/Download.aspx?Command=Core_Download&EntryId=259&PortalId=0&TabId=785
Retrieved: July 7, 2014

The GS1 company prefix would be 030005 for Wyeth Pharmaceutical Division. This would leave five digits to allow for any labeler to identifier up to 100,000 products/packages. These five digits would be used to store the five digits of the product/package number. The following is an example of a GTIN-14 that would be used. (see Figure 53)

Figure 53 GTIN-14 using Company Prefix and Package Code													
GTIN-14													
1	2	3	4	5	6	7	8	9	10	11	12	13	14
0	0	3	0	0	0	5	2	5	0	0	2	3	5

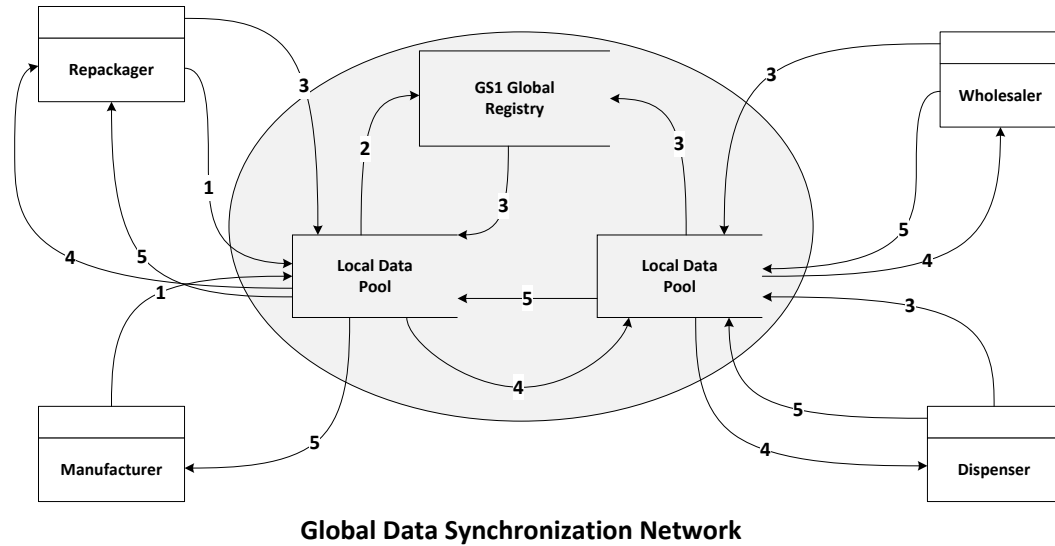
This represents Wyeth's drug called Fibercon that consists of calcium polycarbophil, 625 mg per tablet, and a package is 1 bottle of 140 tablets. To serialize this product, all you would have to do is to add the AI of 21 for serial number and you would have an SNI that could be represented by GS1-128 or 2-D DataMatrix.

Since the FDA NDC is incorporated into the GTIN-14, then any change in the NDC would require a new GTIN-14 to be created. This means any change in the product code or package code of the NDC would require a new NDC and thus, a new GTIN-14. Whenever the package level changes, a new GTIN will be created for the new configuration. This would cover the repackager that might break down a box down to a case or consolidate several cases into a box. If the batch/lot number or expiration date changes, then a new GTIN-14 would have to be created.

3.9.8 DSCSA Product Identifier Verification using GS1 GDSN

Now that the implementation of the DSCSA product verification using GS1 GDSN has been describe at a high level, Figure 54 illustrates what would it look like.

Figure 54 DSCSA Product Identifier Verification using GS1 GDSN



1. **Load data:** Manufacturer or Repackager registers product and company information to its data pool
2. **Register data:** a small subset of this data is sent to the GS1 Global Registry
3. **Request subscription:** Repackager, Wholesaler, Dispenser subscribes to receive Manufacturer or Repackager information
4. **Publish data:** Manufacturer or Repackager data pool publishes the requested information to the requester data pool
5. **Confirm & Inform:** Repackager, Wholesaler, Dispenser sends a confirmation to the Manufacturer or Repackager local data pool which informs them of the action taken by the sending party in using the information.

4. Discussion of the DSCSA Effectiveness

4.1 Introduction

This discussion will focus on whether the DSCSA basic design can prevent counterfeit drugs from entering the USPSC. Using the previously discussed cases of counterfeit drugs entering the USPSC in section 2.5.3.5 of this thesis and some new ones, we discuss how DSCSA will affect those examples of counterfeit drugs entering the USPSC. The scope of the DSCSA only covers the USPSC and would not cover the counterfeit API coming from overseas. However, current FDA rules require that only FDA-approved businesses can make API for U.S. manufacturers. As was determined in the heparin case in section 2.5.3., it was at the tertiary level of suppliers where the counterfeit ingredients were introduced into the heparin API.

DSCSA begins with definitions. DSCSA defines who are trading partners: manufacturer, wholesale distributor, repackagers, dispensers, and third party logistics providers. All these trading partners have to be authorized according to DSCSA. To be authorized, they must be licensed by the state or by the FDA. In addition, the owner of a distributor must be without a felony conviction that relates to dubious behavior related to the USPSC. The rules of dealing with only authorized trading partners would prevent counterfeit drugs from entering the USPSC, such as the case of counterfeit Avastin which started somewhere in the middle east, to a warehouse company in Switzerland, to Germany and England, and then onto the United States wholesale distributors. The requirement of only dealing with authorized trading partners and owners without certain convictions makes the USPSC a closed system. However, as we will discuss in the next section, it doesn't stop an unscrupulous trading partner from getting an API or drug from an unauthorized third

party. The first stop on our discussion is with manufacturers that can introduce counterfeit drugs to the USPSC.

4.2 Manufacturers

In the 1990s Biochimica Opos, an Italian pharmaceutical company which was solely owned by the French pharmaceutical company Roussel-Uclaf, falsified records to conceal its use of unauthorized manufacturing plants in Italy, France, and Romania to produce the antibiotic cefaclor. Cefaclor was eventually recalled and Biochimica Opos withdrew its approved marketing applications (PEW Trusts, 2014).

In 2001, Roussel-Uclaf pleaded guilty to felony charges of conspiracy and defrauding the FDA. Roussel-Uclaf was ordered to pay \$33 million, \$10 million in proceeds and \$23 million as a criminal fine, to the U.S. government. Roussel-Uclaf also pleaded guilty on a two-count indictment charge for selling an adulterated drug in the U.S. market in 1995 and 1996 via Biochimica Opos. Roussel-Uclaf merged with Hoechst in 1997 which later became Aventis Pharma AG by 2001 (PEW Trusts, 2014).

Ranbaxy was FDA approved to manufacture and import drugs into the United States. However, the Ranbaxy's manufacturing plants in India had been selling Guafenesin LA Tablets 600 mg extended release product in the U.S. without FDA approval in 2002. In 2008, the Department of Justice subpoena motion claimed that Ranbaxy had used API from unapproved FDA sites. On February 25, 2009, the FDA prohibited Ranbaxy's APIs and finished products from three manufacturing plants from entering the U.S market. Ranbaxy failed to produce drugs within Good Manufacturing Standards and was found guilty of selling adulterated drugs in the U.S. in 2013, given a fine of \$150 million and had to pay \$350 million in claims for a total of \$500 million (Department of Justice, 2013). On September 16, 2013, an FDA import alert was given for Ranbaxy's Mohali manufacturing plant which

prohibits its drug products from entering the U.S. market (FDA, 2014b). On January 23, 2014, the FDA prohibited Ranbaxy's Toansa plant from manufacturing and distribution APIs for the U.S. market (FDA, 2014b).

Although the above examples are worst case scenarios, every year the FDA issues warning letters for not following good manufacturing practices and adulteration of API and finished pharmaceutical goods in the U.S. and abroad. If the manufacturers of API and finished pharmaceutical products only deal with authorized trading partners, many of these severe problems of bad drugs will not occur. However, in the case of Ranbaxy, it is the culture of the company that has to change.

4.3 Wholesale Distributors

Unscrupulous wholesale distributors have made millions of dollars buying off the gray market and from secondary wholesalers that bought their drugs from non-FDA authorized companies. In 2000 and 2001, Dutchess Business Services, a drug wholesaler licensed in Nevada, and its successor, Legend Pharmaceuticals Inc., bought counterfeit Serostim and later sold it to McKesson Corp. which then sold it to retail pharmacies (Swafford, 2004). In addition, Dutchess and Legend were found guilty of doing business with Florida and South Carolina drug wholesale distributor companies that were not authorized to possess the drugs involved in the transactions (Hardesty, 2014; Swafford, 2004). The person that sold the counterfeit drug, Serostim, to the Florida drug wholesale company, Crystal Coast, who sold it to Dutchess, had been operating a drug wholesale business without license in the state of Florida. Although Florida and Nevada have pedigree laws on the buying and selling of drugs in their states, Dutchess and Legend failed to get and properly maintain appropriate pedigree records from their sellers and provide adequate and correct pedigree information to their buyers. The Nevada Board of Pharmacy fined

Dutchess \$1,000 for each of 399 counts and \$250 for each of the remaining 483 counts for a total fine of \$519,750 (Hardesty, 2014). Legend was assessed a fine of \$250 for each of 125 counts for a total of \$31,250 (Hardesty, 2014). Needless to say, Dutchess and Legend lost their wholesale distributor licenses in Nevada.

One of states that seemed to have a problem with wholesale distributors selling diverted and/or counterfeit drugs was Florida. Florida had a pedigree system that was required for secondary wholesalers but it wasn't enforced (Stovall, 2006). On July 21, 2003, nineteen people were indicted for selling counterfeit drugs (The New York Times, 2003). Eighteen were indicted for a variety of charges from racketeering, conspiracy, and other offenses in regards to prescription drug fraud. The other indictment was on the relabeling of Epogen that indicated a potency that was 20 times greater than its actual potency.

A grand jury was convened in 2003 that and concluded that the Florida wholesale pharmaceutical industry had become corrupt due to criminal elements (Stovall, 2006). Some Florida drug wholesalers who had been given licenses to operate in Florida had one or more felony convictions (Hileman, 2003). In addition, many of those Florida drug wholesalers did not have the proper training or experience to handle, store, or deal in pharmaceuticals (Hileman, 2003). Additionally, according to the grand jury report, corrupt secondary wholesalers in Florida had done business with millions of dollars of prescription drugs that were later to be found counterfeit (Stovall, 2006). Counterfeiters used relabeling, dilution, substitution, and overstating the potency techniques when counterfeiting the drugs.

In 2005, three businesses and eleven individuals were charged with a \$42 million dollar conspiracy to distribute counterfeit and misbranded Lipitor smuggled into the United States from South America and the distribution of a stolen drug (NABP, 2013). None of this

would have occurred without corrupt wholesale drug distributors that helped in the distribution of these drugs. This case caused the recall of 18 million Lipitor tablets.

In 2012, there were two cases that resulted in over a billion dollars in fraud due to drug diversion that covered multiple states where 71 people and three corporations were charged (NABP, 2013). Drugs that were dispensed to Medicaid patients were diverted and resold back to corrupt wholesalers, who then sold the drugs to pharmacies. The drug diversion occurred from 2007 until 2011, and although fraudulent drug pedigrees were supplied, it was impossible for the chain and independent pharmacies to trace a pedigree to determine a place of origin (NABP, 2013).

The current case of Avastin and Altuzan further indicts the wholesale distributor that is willing to cut corners to make a buck which in turn can cause loss of life. In most cases, dealing with only authorized trade partners will prevent the introduction of counterfeit drugs into the USPSC. In DSCSA, verification is not only with the seller but with the manufacturer or repackager. In a Nevada case of counterfeit drugs, it wasn't until the manufacturer was contacted before it was determined by the lot number that the drugs were counterfeit (Swafford, 2004). Furthermore, by contacting the manufacturer, a determination on whether the seller is authorized to sell the drug becomes known. The database of authorized wholesale distributors which is maintained by the FDA will help trading partners to determine authorized wholesale distributors. In many of these cases given, the main theme was that none of the incidences were found through inspections but through serendipitous means or after the fraud was committed and discovered.

4.4 Pharmacy and Pharmacist

Counterfeit, diverted, and diluted drugs do enter the USPSC via corrupt pharmacies or pharmacists. One of the above cases is of a pharmacy or pharmacist accepting drugs

without known provenance. Another crime that is investigated by the FDA OCI has to do with the pharmacy or pharmacist selling free samples that the pharmaceutical sales representative gives to the pharmacy or pharmacist to give to licensed physicians (FDA, 2011). In this example, the pharmacist or pharmacy keeps the drug and sells it to their customer for a nice profit. When the pharmacy or pharmacist bills the insurance company or Medicare or Medicaid for the free samples, you can add health care reimbursement fraud to the indictment.

There is a case of a licensed pharmacist buying counterfeit drugs, Cialis and Viagra, from China for his pharmacy in San Jacinto, Texas (FDA, 2011). His order was 1000 tablets of counterfeit Cialis and 4500 tablets of Viagra which cost him 30 cents per tablet for a total of \$1650. At that time, the wholesale price per pill for Cialis was \$9.55 and \$13.55 for Viagra which would provide him with a net profit of \$68,875. The special agents of Immigration and Customs Enforcement (ICE) and FDA OCI were involved with this purchase by posing as deliverymen. The licensed pharmacist was sentenced to two years in federal prison without a chance of parole.

In Kansas City, MO for ten years, 1992 to 2002, a pharmacist and owner of two pharmacies, Robert Courtney, diluted over 98,000 prescriptions written by 400 physicians (Belluck, 2001; Elliot, 2002). Some of the drugs that were diluted were anticancer drugs: Taxol and Gemzar. The rest is unknown as Robert Courtney's spurious deeds were completed intermittently with no records kept. Lawsuits were filed against the pharmaceutical companies of Eli Lilly and Myers Squibb which settled out of court for \$72 million (Potent Settlement for Drug Dilution Case.2003; M. Morris, 2013).

DSCA clearly states that business must be completed between authorize trading partners, transaction records must be exchange between buyer and seller that goes back in

history to the manufacturer, and product identifiers are to be verified with the manufacturer or repackager. If the pharmacy or pharmacist follow those rules, the drugs they sell will be good. However, it really doesn't cover personal criminal acts which are covered by federal and state laws.

4.5 Physicians and Healthcare Providers

Physicians and healthcare providers have been involved in distributing counterfeit, diverted, and diluted drugs. DSCSA doesn't regulate physicians and healthcare providers as they are regulated by the states. Because the physicians and healthcare providers are regulated by the states, each state or group of states needs to pass laws that would require physicians and healthcare providers to buy from authorized trading partners in accordance with DSCSA.

5. Conclusion

Although many of the details of the DSCSA will be worked out in the next ten years, DSCSA basic structure and requirements should be adequate enough to reduce the probability of counterfeit drugs from entering the USPSC. The requirement of obtaining drugs only from FDA authorized trading partners will prevent counterfeit drugs from the gray market from entering the USPSC. Verification of the drugs received by the buyer through the manufacturer and repackager should identify potential counterfeit drugs at their point of origin into the USPSC. The requirement of transaction records that go back to the manufacturer before accepting the drug should further make it more difficult for counterfeit drugs to enter the USPSC. Vigilance by the FDA will be very important in making sure the USPSC is secure. DSCSA doesn't mitigate the actions of the unscrupulous manufacturer, wholesale distributor, pharmacy, and pharmacist but it does make it harder for their efforts to succeed.

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VITA

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Degree Awarded: Bachelor of Arts in Business, MIS, Finance, and Economics, 2008,
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Professional Experience:

Consultant/Contractor August 1990 to December 2007

Clients: Digital Equipment Corp., GTE Mobile Communication, Bell Atlantic Tricom Leasing Co., Navistar International, Apple Computer Inc., Owen Corning Science and Technology, Cellular One, Ethicon Endo-Surgery, Sybase, Pfizer Inc., Fleet Bank, Sabre, VoiceStream, Eastern Washington University

Summary: I have designed, installed, maintained, trained, analyzed, documented, and performed project management in the OpenVMS Cluster and Non-Cluster environments in a multitude of configurations pertaining to systems (VAX and Alpha) and applications (Banking, Telecommunication Finance and Billing, Pharmaceutical, and Medical) using RMS, Oracle RDB and RDBMS, MS Word, MS Excel, and MS Access over the past 12 years for several vendors. Programming languages are SQL, Fortran, Basic, Pascal, and DCL using MMS and CMS as tools for version control. My Software Configuration experience has been to design, setup, support, and manage a Development, Test, Production Support and Production environments using CMS and MMS as the software version control and build mechanisms, which included Common Data Dictionary (CDD). I have used MS Project for project management and proposals.

System Manager and Programmer December 1984 to August 1990

Clients: Sierra Health Services, Anchorage School District, and Eastern Washington University

Summary: For the above companies I performed the duties of a System Manager, RMS DBA, and programmer/analyst in a cluster and non-cluster environments using MS Office tools for analysis of performance and documentation.

Geophysicist June 1979 to May 1984

Clients: St. Joe American Corp. and Cominco American Inc.

Summary: For the above companies, I was a Geophysicist that performed field duties along with being a System Manager and programmer/analyst performing data analysis and modeling.