FOOD, DRUGS, AND CIGARETTES: THE INFLUENCE OF POLITICS ON FDA REGULATIONS

by

JOY ELLEN MAY SHERRICK

(Under the Direction of Paul J. Brooks)

ABSTRACT

This thesis will examine the evolution of historical attempts to regulate tobacco from the late nineteenth century to present day. The influences of politics and societal impact on FDA regulations of the tobacco industry have been the subject of considerable ongoing controversy. This challenge stems from the FDAôs attempts to assert jurisdiction for regulating an industry that constitutes a significant portion of the American economy. Although the scope of the FDAôs jurisdiction clearly covers food, drugs, cosmetics, devices and biological products, the agency has not historically been given the latitude to place cigarettes into an appropriate classification, greatly inhibiting any attempts towards implementing complete regulatory authority. Despite the recent tobacco acts enacted on behalf of the FDA and the current Obama administration, tobacco continues to be the single most preventable cause of death, disease and disability in the United States today.

INDEX WORDS: Tobacco, Cigarettes, FDA Regulations, Smoking

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DEDICATION

I dedicate this work to the memory of Dr. Harvey W. Wiley, who like myself, humbly grew up on a farm in Indiana, and became inspired to study Chemistry while working on the family farm, planting and harvesting crops and caring for the animals. To my Dad, a farmer who never had the opportunity to pursue a college degree, yet is the wisest individual, smartest scientist, engineer and politician I have ever known. Additionally, to my supportive High School Chemistry teacher, Bob, who inspired me to love science and pursue this lifelong educational journey. Finally, to my loving daughters and husband, thank you for all of your continued support and encouragement which has brought me to this place today.

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CHAPTER 1

INTRODUCTION

1.1 BACKGROUND

As far back as 1612, when John Rolfe conducted an experiment on tobacco cultivation in Virginia, tobacco use has resulted in social, economic and medical ramifications.

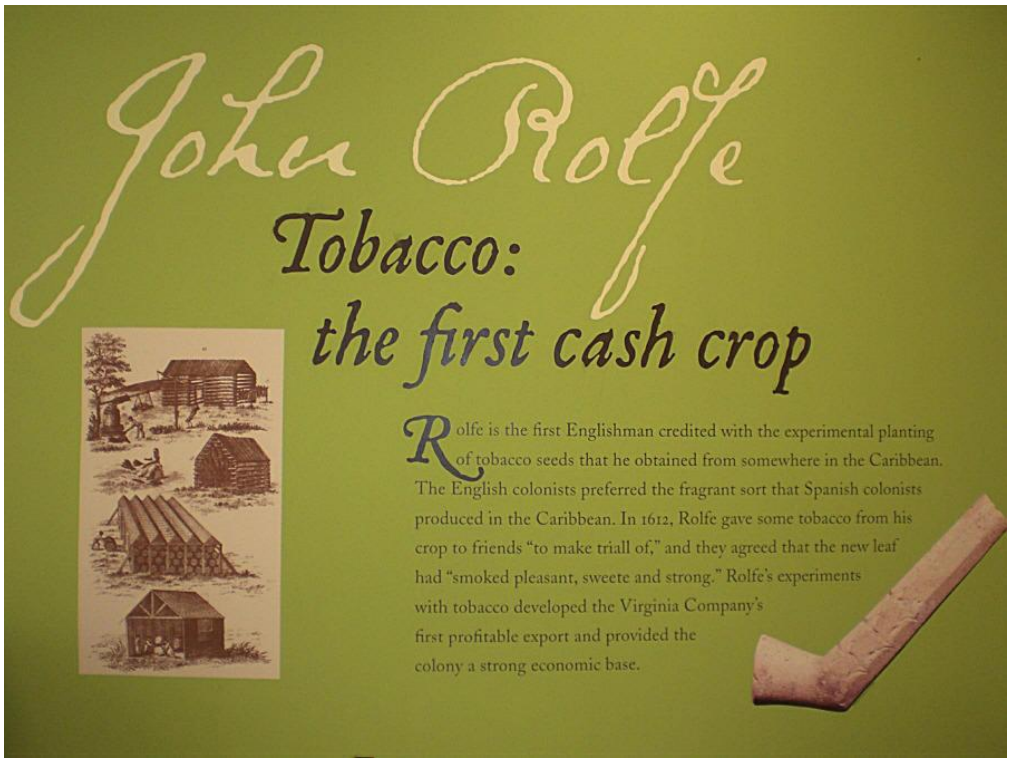

Figure 1: http://jamestownechesapeakebaycompany.com/Henricus_John_Rolfe.jpg

As a result, tobacco has been subjected to a plethora of various regulations over the past 400 years. Since then, tobacco use has been implicated by society and the medical community for the damage it has done to both the social and physical condition of mankind. Yet, tobacco use still continues to provide a significant source of revenue to the state and Federal governments of the United States. (Table 1: State and Local Tobacco Tax Revenue, Selected Years 1977-2009).

TABLE 1:

State and Local Tobacco Tax Revenue, Selected Years 1977-2009
[Thousands of Dollars]

Region and State	1977	2008	2009
United States	**3,631,728**	**16,570,640**	**17,157,014**
New England	**303,262**	**1,265,382**	**1,437,335**
Connecticut	75,084	334,907	316,246
Maine	24,296	150,499	144,425
Massachusetts	142,759	436,942	587,331
New Hampshire	27,130	169,789	195,034
Rhode Island	24,393	113,998	130,503
Vermont	9,600	59,247	63,796
Mideast	**890,333**	**3,437,803**	**3,758,644**
Delaware	12,246	125,337	125,505
District of Columbia	12,514	23,900	37,620
Maryland	54,349	376,112	405,558
New Jersey	168,780	789,351	766,142
New York	394,478	1,097,281	1,434,103
Pennsylvania	247,966	1,025,822	989,716
Great Lakes	**666,999**	**3,863,597**	**3,846,833**
Illinois	193,944	827,484	770,648
Indiana	51,521	519,871	510,585
Michigan	140,271	1,076,087	1,043,532
Ohio	196,910	954,685	928,493
Wisconsin	84,353	485,470	593,575
Plains	**281,535**	**1,076,745**	**1,057,881**
Iowa	46,277	252,857	238,153
Kansas	32,108	118,253	112,943
Minnesota	83,802	419,127	422,780
Missouri	79,141	122,999	121,130
Nebraska	22,610	75,479	70,438
North Dakota	8,570	24,127	24,114

South Dakota	9,027		63,903	68,323
Southeast	**646,660**		**2,278,796**	**2,387,221**
Alabama	58,361		175,829	170,990
Arkansas	46,066		147,482	171,038
Florida	186,448		443,732	447,061
Georgia	74,593		233,158	229,673
Kentucky	22,253		178,558	214,597
Louisiana	56,954		145,578	145,578
Mississippi	31,072		58,327	83,589
North Carolina	20,308		248,159	243,370
South Carolina	23,575		31,073	30,573
Tennessee	67,881		272,433	301,219
Virginia	31,121		229,798	234,438
West Virginia	28,028		114,669	115,095
Southwest	**388,689**		**2,157,244**	**2,231,528**
Arizona	35,497		407,420	373,882
New Mexico	13,683		48,235	41,619
Oklahoma	51,960		254,694	259,234
Texas	287,549		1,446,895	1,556,793
Rocky Mountain	**65,119**		**465,144**	**452,769**
Colorado	33,242		226,735	223,805
Idaho	7,997		54,781	52,918
Montana	11,528		94,020	89,776
Utah	7,680		62,246	59,821
Wyoming	4,672		27,362	26,449
Far West [1]	**373,969**		**1,840,517**	**1,800,225**
California	271,504		1,037,457	1,000,456
Nevada	11,130		134,617	119,566
Oregon	31,817		254,955	248,205
Washington	59,518		413,488	431,998
Alaska	4,851		96,147	96,433
Hawaii	10,311		89,265	88,145

[1] Alaska and Hawaii are excluded from the Far West regional totals, but are included in the U.S. totals.

Source: State & Local Government Finance Data Query System. http://www.taxpolicycenter.org/slf-dqs/pages.cfm. The Urban Institute-Brooki
Data from U.S. Census Bureau, Annual Survey of State and Local Government Finances, Government Finances, Volume 4, and
Census of Governments (1977-2009). Date of Access: (5-Dec-11 5:13 PM).

Similarly to alcohol, tobacco has routinely been subjected to regulatory controls of the quantity and quality of production. However, the laws pertaining to tobacco have historically been much more lenient than those for alcohol. For example, there has never been a time when tobacco was completely prohibited throughout the United States to the degree that was seen with alcohol during the Prohibition era of 1920 ï 1933. It has taken nearly 75 years since then to see cigarette use prohibited only under limited circumstances and at various times in different jurisdictions such as with commercial airline flying, movie theaters, New York City restaurants, etc. (Appendix A: American Lung Associationôs Battle Against Tobacco Use Milestones ï Tobacco Timeline). Tobacco use today includes the smoking of cigarettes, pipes, cigars, snuffing and chewing. However, up until around the year 1870, cigarettes were relatively rare in the United States, and relatively all of the tobacco utilized domestically was chewed during the mid-19th century.[1] Irregardless of the mode of consumption, tobacco has always been the subject of controversy and debate with respect to the appropriate governmental regulatory attitude. For example, proponents of tobacco have stressed its economic and industrial significance, and recent studies even suggest the alleged psychological and neuroprotective benefits of smoking in schizophrenia, Alzheimerôs disease and Parkinsonôs disease.[2] Those opposed to tobacco can cite the proven health hazards of smoking and the ramifications of second hand smoke on the innocent bystander, all of which have been the subject of ongoing landmark litigation against the tobacco industry. In 1994, one such litigation launched the beginning of the first public glimpse of the tobacco industry documents which have now become the largest repository of internal information pertaining to the marketing, manufacturing and research activities of tobacco

companies. It began with a series of articles that was published in the New York Times based on information from Brown and Williamson Tobacco Corporation and its parent company, the British American Tobacco Company. These tobacco industry documents, which had been confiscated by a tobacco industry inside whistleblower, were also sent to a university professor who then published them into peer-reviewed academic articles, a book and also resulted in the documents being posted on the internet.[3] On May 12, 1994, a box of tobacco company documents was delivered to Professor Stanton Glantz at the University of California, San Francisco. The documents in the box dated from the early 1950s to the early 1980s, and consisted of confidential internal Brown and Williamson documents, including internal discussions of the tobacco industry's public relations and legal strategies over the years. These documents were stamped with a "confidential" or "privilegedò header, and the return address listed on the box was from a "Mr. Butts."Soon afterwards, the news media began airing stories based on these internal documents from Brown and Williamson. These internal documents became the subject of hearings held on June 23, 1994, before the US House of Representatives Subcommittee on Health and the Environment. Additional documents were made available during subsequent Congressional hearings[4], and during subsequent tobacco litigation cases.[5] These tobacco documents were also valuable in the settlement of a suit by the state of Minnesota and Blue Cross/Blue Shield against the major tobacco companies. The Minnesota settlement contained a provision allowing for Attorney General Humphrey to require that the tobacco industry defendants release millions of pages of internal documents. This resulted in the Tobacco Master Settlement Agreement (MSA) which was entered in November 1998, originally between the four largest United States tobacco companies

(Philip Morris, R. J. Reynolds, Brown & Williamson and Lorillard) and the attorney general of 46 states. The states settled their Medicaid lawsuits against the tobacco industry for recovery of their tobacco-related health-care costs, for the sum of $206 billion dollars over a twenty-five year period. However, the agreement exempted the companies from private tort liability regarding harm caused by tobacco use.[6] The main purpose of the Master Settlement Agreement (MSA) was to impose regulatory measures on the tobacco industry as it pertains to advertising and public disclosure. As a result, the tobacco industry was required to release all documents that were not considered attorney/client privileged or containing any trade secrets. The University of California in San Francisco, now houses an online searchable digital library (http://legacy.library.ucsf.edu) of tobacco documents from around the world, totaling more than 14 million documents by major tobacco companies related to their advertising, manufacturing, marketing, sales and scientific research activities. [7] The University of Georgia also has a website (http://www.tobaccodocs.uga.edu/) dedicated to the ñTobacco-Documents Projectò, which was a three-year linguistic investigation into the stylistics of deception and manipulation in tobacco-industry documents, which was made possible by a grant from the National Cancer Institute (1 RO1 CA87490-01, July 1, 2001 to June 30, 2004).[8] These tobacco documents have since been used for subsequent litigation against the tobacco industry, as well as revealing numerous unethical practices of the tobacco industry thereby supporting efforts towards tobacco control policy. (Table 2).

TABLE 2: Selected findings from the tobacco industry documents

Tobacco industry motives

- Profit
- Fear of litigation
- Protect tobacco from regulation
- Concerns about credibility/image of the industry

How the tobacco industry operates

- Deceive the public and policy makers
- Hide information from the public and policy makers
- Create controversy
- Involve lawyers in decisionsð from scientific research to marketing to public relations
- Use third parties or front groups to hide political lobbying and public relations activities
- Coordinate action and communication among tobacco companies globally
- Some disagreement among tobacco companies in different countries regarding how
  to deal with fact that tobacco is harmful
- Influence practices/procedures that affect a variety of corporate interests
- Use financial ties with other corporations to pressure those organizations to support
  tobacco industry goals

The truth about tobacco and tobacco advertising

- Nicotine is a drug
- Nicotine is addictive
- Secondhand smoke exposure is harmful to health
- Industry attempts to develop less harmful tobacco products have been a failure
- Tobacco advertising, promotions, and product design target youth
- Tobacco advertising aims to increase consumption of tobacco products

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Bero, L., ñImplications of the Tobacco Industry Documents For Public Health and Policyò, Annu. Rev. Public Health 2003. 24:267-88. (Dr. Bero assisted Dr. Stanton Glantz in the analysis of the B&W documents at UCSF). See also: Glantz, Stanton A., John Slade, Lisa A. Bero, Peter Hanauer, and Deborah E. Barnes, editors *The Cigarette Papers.* Berkeley: University of California Press, c1996 1996. http://ark.cdlib.org/ark:/13030/ft8489p25j/

1.2 PROPOSAL

The main question to ask is, ñWhat are the political influences which have led to the current FDA tobacco regulations?ò The widespread motivation for tobacco regulation has come from all sides of the controversy. Although earlier restrictions were influenced by various groups convinced of the immorality of smoking, in their attempts to suppress a sinful habit, current day regulations are more politically focused around finding ways to balance the social tolerability of this habit, while maintaining the economic benefit and simply monitoring and reducing its adverse side effects.

I will first provide a historical overview of the timelines associated with tobacco utilization and regulations in Chapter Two, and answer the question, ñHow far have we come?ò Important regulatory timelines and milestones will be discussed, specifically addressing the FDAôs dilemma with the challenge of the classification of cigarettes as either a drug or device. The economic importance placed on tobacco and politics influencing regulations will be debated, along with the health care consequences.

Chapter Three will discuss the perspective of Dr. David Kessler, including his book, (Kessler, David A. (2001). *A Question of Intent: A Great American Battle with a Deadly Industry)*, as well as an interview conducted with Dr. Kessler on November 12, 2012. The tobacco documents that Dr. Kessler mentions from the Master Settlement Agreement (MSA) and the http://tobaccodocuments.org/ website will also be included in this chapter, along with excerpts from his discussions with tobacco industry informants.

Chapter Four will address the main question, ñWhat are the political influences which have lead to the current FDA tobacco regulations?ò Despite the passage of the Family Smoking Prevention and Tobacco Control Act of 2009, which was touted to be an ñhistoric effortò on behalf of the FDA to curb the hundreds of deaths caused by tobacco each year, why do tobacco deaths and associated disease continue to rise? [9] Tobacco use is said to be the single most preventable cause of disease, disability, and death in the United States. Each year, an estimated 443,000 people will die prematurely from smoking or from the exposure to secondhand smoke, and another 8.6 million will live with chronic or serious illness caused by smoking. Despite these risks, approximately 46.6 million U.S. adults still continue to smoke cigarettes.[10] Why doesnôt the FDA do more to stop the nationôs number one killer?

Secondhand smoke exposure is also the cause of death, serious disease, including heart disease and lung cancer in nonsmoking adults, and sudden infant death syndrome, acute respiratory infections, ear problems, and severe asthma attacks in children. It is estimated that primarily because of exposure to secondhand smoke, there will be 3,000 nonsmoking Americans who will die of lung cancer, more than 46,000 will die of heart disease, and about 150,000ï 300,000 children younger than 18 months will have lower respiratory tract infections.[11]

Of additional importance, is the question of the increased healthcare costs associated with smoking. The significant economic burden of tobacco use is estimated to be more than $96 billion a year in medical costs and another $97 billion a year from lost productivity.[12] If the FDA truly has the authority to regulate tobacco, then why are these healthcare costs

increasing each year? Why also do we continue to see an increase in tobacco tax revenue each year? (Table 1). And why was the nationôs largest cigarette manufacturer ñthrilledò, when President Obama signed the Family Smoking Prevention and Tobacco Control Act?[13]

To summarize and answer all of these questions, this thesis will examine the evolution of significant attempts by the FDA to regulate tobacco from the late nineteenth century to present day. I will provide some background into the early history and chemistry of the tobacco plant constituents, along with the invention of flue-curing which ultimately led to the dangerous inhalation of tobacco. A glimpse into the early perspective of Dr. Harvey Wiley will be presented, along with references to Dr. David Kesslerôs contribution towards current tobacco regulations, up to and including the Tobacco Control Act signed by President Obama. This paper will compare and contrast the legal and cultural definitions of ñdrugò, and explore the historical challenges that the FDA has faced when trying to invoke this literal definition into its efforts to regulate tobacco. Finally, this thesis will examine the political and economic considerations which have greatly influenced the limitations of the FDAôs authority in fully regulating tobacco.

1.3 METHODOLOGY:

The historical research methodology which I have employed for this thesis has involved an extensive on-line search of the Legacy Tobacco Documents Library, accessible to the public at: http://legacy.library.ucsf.edu. The Legacy Tobacco Documents Library is the largest tobacco industry archive in the world, as part of the 1998 Master Settlement Agreement between the tobacco companies and the attorney general of forty-seven states. The Legacy Tobacco Documents Library currently houses over 17,008, 922 documents and 81,253,444 pages of information.[14] Most documents are full-text searchable, with options to search by terms like ñcancerò, expressions like ñcauses cancerò, or ñFDA interviewò. I have located much of the information for this thesis by searching for terms such as, ñFDA regulationò, ñtobacco plantò, ñflue-curedò, ñKesslerò, ñFDA Policyò, ñtobacco adsò, ñsafe cigaretteò and ñpesticideò. By using a snowball sampling strategy, I was able to use the retrieved material to identify additional search terms, such as names of scientists or researchers for a specific analysis for example, òsupercritical extraction.ò Snowball sampling is a non-probability sampling technique that is based on the judgment of the researcher, and has become the gold standard research methodology for searching the legacy online tobacco documents.[15] Because of the non-probability and qualitative nature of this research technique, it differs from quantitative and probability based sampling in that it is not possible to make statistical inferences from a sample that can be generalized to a population, nor can the samples be randomized.[16]

The following steps outline the snowball sampling strategy:[17]

- Previous searches inform subsequent searches
- Researcher builds a relevant collection of documents by reading and analyzing search results.
- Researcher conducts snowball searches based on the contents of the documents returned in the initial searches.
- Broad research questions are used to guide the initial searches of the document collections.
- Qualitative analysis of the contents of documents guides the researcher to refine research questions and continue the search process.

These searches yielded thousands of documents, and a limitation of my analysis is the resulting volume and indexing issues of the documents. For those reasons it is impossible to ensure that I have located all potentially relevant documents. However, the documents I have retrieved by this research methodology have provided substantial insight into the industry attempts to influence the FDA regulatory jurisdiction of tobacco.

The University of Georgia Tobacco Documents Corpus TDC Text Analysis online Toolkit, http://www.tobaccodocs.uga.edu/, was also a useful database in searching for related research reports and publications. For example, in his 2008 dissertation of the University of Georgia Tobacco Documents Corpus (Kretzschmar et al 2008), Dr. Clayton Darwin points out that these tobacco documents have become an important research data source for business ethics and policy making[18], language and deception[19], business methods[20], business litigation[21], and biochemistry.[22] These references were helpful in providing insight into additional terms and phraseology to supplement and narrow down subsequent online search efforts.

The www.fda.gov website provided the primary searchable database for the current regulations and guidance documents pertaining to the history and timelines of the FDAôs attempts to regulate tobacco, tobacco products and cigarettes. This website was particularly helpful in researching the authentic and certified copy of the 2009 Tobacco Control Act signed by President Obama, which provides much of the discussion for Chapter Four of this thesis. Specifically, my searches were performed in this document to answer the questions of GMP regulations, (and the lack thereof), for tobacco manufacturers, as well as questions pertaining to the New Tobacco Product Review and Evaluation process. In particular, the Premarket Tobacco Application process, the Substantial Equivalence Report and the Exemption from Substantial Equivalence Request process were examined to answer the main question regarding the scope and current limitations of the FDAôs authority on regulating tobacco.

The WHO Framework Convention on Tobacco Control (WHO FCTC) website: http://www.who.int/fctc/text_download/en/index.html , provided insight into the global regulatory strategy to address the tobacco epidemic and provided new legal dimensions for international health cooperation. Additional resources within the WHO website included a manual on searching the tobacco industry documents online: ñThe Tobacco Industry Documents ï What They Are, What They Tell Us, and How To Search Themò. http://www.who.int/tobacco/communications/TI_manual_content.pdf[23]

CHAPTER 2

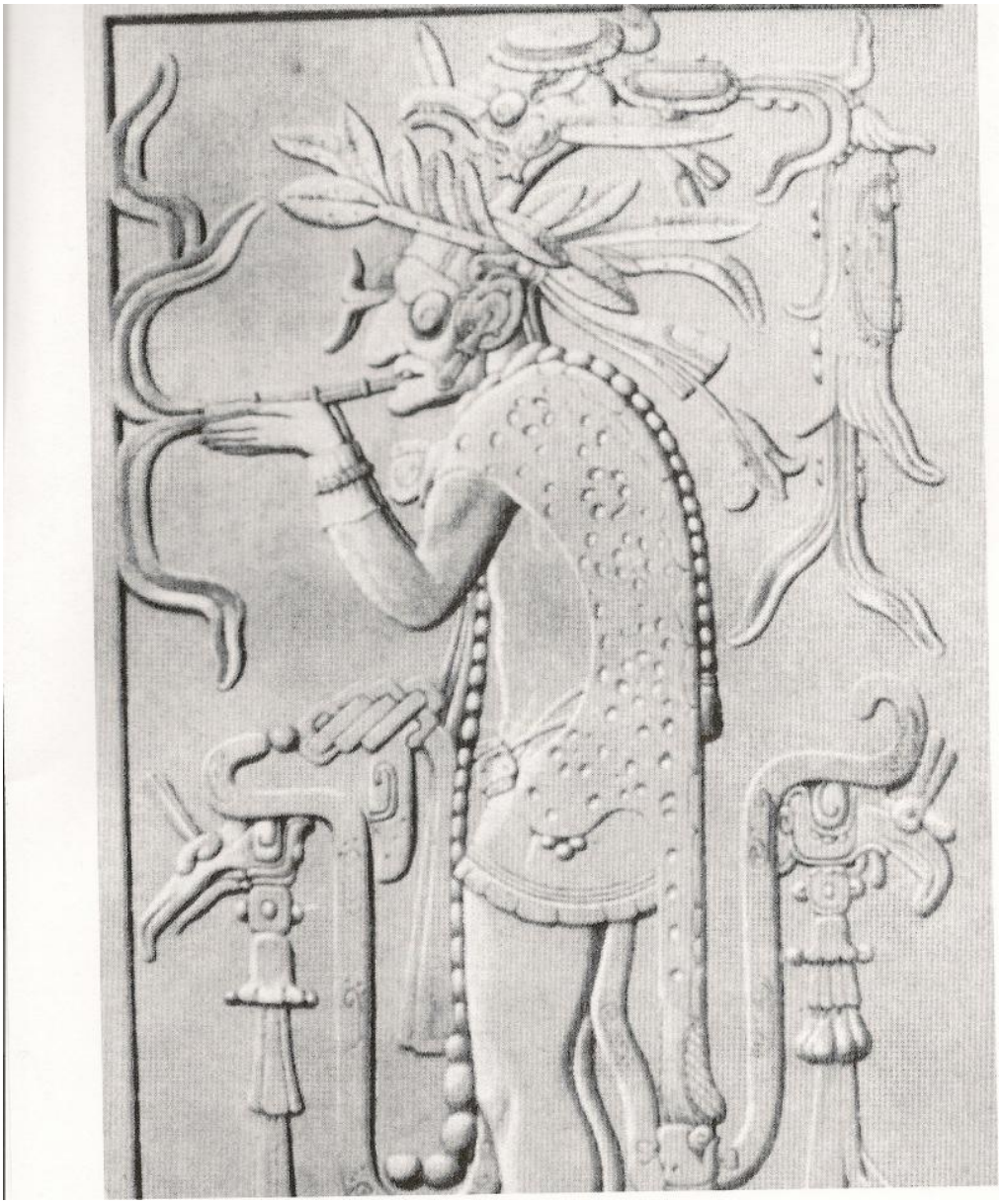
HOW FAR HAVE WE COME?

2.1 HISTORY OF TOBACCO UTILIZATION

To fully understand the current scope and magnitude of tobacco and its political power to control its own self regulation, it is important to first learn about the history of tobacco utilization, the chemistry of the tobacco plant and nicotine, as well as the evolution of cigarette manufacturing and the development of industry marketing strategies.

Trace amounts of nicotine may be found in some prehistoric plants, including belladonna[24] and *Nicotiana africana*, and nicotine metabolites have been found in human remains and pipes unearthed in the United States and in Africa.[25] Habitual tobacco use was an important social practice of Native Americans during the Historic Period, however the prehistoric origins of this practice are poorly understood.[26] There is evidence of the use of tobacco in a smoking pipe from a prehistoric cemetery in Boucher, Vermont dating to the first millennium B.C.[27], and tobacco has been found that dates to the Pleistoncene Era around 2.5 million years ago in a small block of fossilized tobacco in the Maranon river basin of northeastern Peru.[28] It is believed that the Guatemalan Mayas introduced smoking tobacco to the Toltec Aztec Empire in Mexico around the year 470 to 630 A.D., however the first known pictorial evidence of smoking was found on an 11th century Guatemalan pottery vessel which depicts a Mayan Indian smoking a roll of tobacco leaves tied with a string.[29] The Mayan Indian in the depiction is believed to be an elderly priest smoking tobacco for a religious ceremony. (Figure 2)

The custom of making smoke offerings was already believed to be hundreds of years old by this time.[30] Figure 2: http://www.pdocigars.com



The Mayan hieroglyphics depict both the tobacco plant and various smoking rituals in which the gods revealed themselves in the rising smoke.[31] Historians believe that the Central and South American Indians began finding ways to use tobacco for religious as well as medicinal practices such as a cure-all, wound dressing, and analgesic. Tobacco

was not only smoked, but chewed, snorted and even drunk in a liquid concentrate. The Indians of South America were believed to be the first to domesticate tobacco and they also discovered novel approaches to using it according to Johannes Wilbert, an expert on the use of tobacco by the Indians who said that they, ñchew tobacco quids, drink tobacco juice and syrup, lick tobacco paste, apply tobacco enemas, snuff and smoke. In addition, they administer tobacco products topically to the skin and to the eye.ò[32] The Las Casas manuscript of the voyage of Christopher Columbus, describes the gifts that the Indians presented upon his 1492 arrival in the New World: ñNatives brought fruit, wooden goods, and certain dried leaves which gave off a distinct fragrance.ò[33] Columbus accepted the gifts and ordered them brought back to the ship where the fruit was eaten, but the pungent "dried leaves" were thrown away. Around the 1492 timeframe of the inaugural Columbus voyage, Rodrigo de Jerez and Luis de Torres observed the Cuban Indians wrapping dried tobacco leaves in palm or maize similar to a òmusket formed of paper, and after lighting one end, they commenced to drinking smoke through the other.ò[34] Jerez later became a smoker himself, and brought the habit back to his Spanish hometown. However, the smoke billowing from his mouth and nose frightened his neighbors so much that he was imprisoned by the holy inquisitors for 7 years.[35] By the time he was released, smoking had become widespread throughout Spain. Early medicinal uses for tobacco smoking date as far back as 1568, when the Frenchman, Andre Thevet wrote that tobacco smoking cleaned the "superfluous humours of the brain". [36]In 1571, the German physician, Dr. Michael Bernhard Valentini, wrote in his *Polychresta Exotica* (Exotic Remedies) that tobacco smoke was good for the treatment of colic, nephritis, hysteria, hernia and dysentery, and described various tobacco enemas to treat these disorders.[37]In

1577, John Frampton provided the English translation of the Spanish survey originally written by Nicolas Monardes, which recommended tobacco use for toothache, falling fingernails, worms, halitosis, lockjaw and cancer.[38] There are also eighteenth-century methods of reviving drowning victims by ñblowing tobacco smoke up the anusò.[39] The first historical indications of tobaccoôs harmful effects date back to the early 1600ôs. In 1603, English physicians complained to King James that tobacco was being used without a prescription. As a result, in 1604, King James wrote, ñA Counterblaste to Tobaccoò, and subsequently raised the tobacco import tax by 4,000%.[40] This tax increase put a halt to most people buying tobacco, but unfortunately, depleted the funds which had been filling up the Treasury. King James promptly cut the taxes and the money soon came pouring back in. This was perhaps one of the first lessons learned in tobacco economics, proving that one can profit from the very thing one despises. This treatise is considered one of the most famous and historical tracts opposing the social use of tobacco, which James described as a habit adopted from ñun-baptized barbariansò. [41] The passages describe King Jamesô observance of the autopsies of smokers, noting that the smokersô ñinward partsò (lungs and brains), were ñinfected with an oily kind of sootò.[42] In regards to second-hand smoke, James suggested that, ñThe wife must either take up smoking or resolve to live in a perpetual stinking tormentò.[43]In 1612, following King Jamesô Counterblaste on Tobacco, John Rolfe raised Virginiaôs first commercial crop of tobacco. Tobacco was being used as currency in the early 1600ôs, and in 1619, the first shipment of English women arrived in Jamestown for a prospective husbandôs payment of 120 pounds of tobacco.[44] The price increased to 150 pounds of tobacco per wife in 1621, and the clergyman performing the wedding ceremony was also paid by a substantial quantity

of tobacco.[45] An important distinction of tobacco utilization throughout early history is that tobacco was smoked, chewed, snorted and ñdrunkò for ritualistic purposes as seen by the Mayans and North American Indians, and then later smoked and chewed by members of English and North American Colonial society. However, smoking was not yet completely ñinhalableò, or in cigarette form. The cigarette was actually a nineteenth-century invention, when in 1832, an Egyptian cannoneer smoked rolled tobacco from paper tubes which had been used for gunpowder.[46]Before this time, tobacco was generally not drawn into the lungs, but typically only ñpuffedò through the mouth and nose via pipe or cigar, (unless it was drank as a liquid or administered as an enema as mentioned earlier). From a chemical perspective, when smoking a cigar or pipe, the smoke is taken only into the mouth, where the nicotine then passes through the lining of the oral membranes and into the bloodstream. The smoke from a cigar or pipe is very alkaline, so it is too harsh and irritating to inhale, otherwise the coughing mechanism is quickly and easily triggered. Additionally, the flavor of a pipe or cigar is enjoyed by puffing, instead of inhaling the smoke. That is why smoking a pipe or cigar takes 45 minutes to an hour vs. a cigarette which can be smoked in a few minutes.[47] Cigarettes were viewed as a ñsnackò, and pipes or cigars were viewed as a ñmealò, so cigarettes could be consumed without taking a break from work.[48] This is an important milestone in the history of tobacco utilization, along with the accidental discovery of flue-curing in 1839 by a Negro slave who used charcoal to cure tobacco.[49]Since the charcoal burned much hotter than the wood typically used to cure tobacco, the leaves turned a bright golden yellow color and smoked milder than usual. This discovery led to the widespread production of the new bright-leaf tobacco throughout the tobacco states. Flue-curing

tobacco fetched a higher price in the marketplace, and also had the advantage of causing less barn fires than was seen with wood curing, as well as the tobacco no longer tasted like the woody smoke fumes.[50]The important consequence of this improvement in smokability, was that cigarettes were now more easily inhalable, and unfortunately now more deadly.[51]From a chemical perspective, flue-curing alters the basic chemistry of the tobacco leaf by increasing its natural sugar content. The green tobacco leaf contains a large amount of starch, which then converts into sugar during the initial ñyellowingò stage of the curing process.[52]After four days into the flue-curing process, the heat is cranked up high enough to deactivate the natural enzymes that would typically ferment or degrade the sugars in tobacco as seen in the wood curing process, which results in a 20% higher sugar content, and a milder, less alkaline smoke. The sugars then convert to acids when burned, neutralizing the bases generated with the combustion of the leaf proteins, amino acids, and the nicotine alkaloid itself. [53]The cigarettes made from flue-cured tobacco are more addictive than pipes or cigars, because the lungs are more effective conduits of nicotine than the membranes and tissues lining the orifices of the mouth. Since the lungs have a surface area approximately the size of a tennis court, there is ample opportunity for nicotine to be widely distributed and absorbed. Unfortunately, this large surface area becomes a fertile breeding ground for emphysema, bronchitis and even cancer since more cells are proportionately exposed to carcinogenic tars.[54]

The importance of the sugar content of flue-cured tobacco was a landmark discovery impacting the ongoing history of tobacco utilization. According to one tobacco industry insider, ñWere it not for sugar, the American blended cigarette and with it the tobacco industry of the United States would not have achieved such tremendous development as it

did in the first half of this centuryò.[55] The discovery of flue-curing also created an opportunity for tobacco manufacturers to incorporate the cheaper burley tobacco variety, which normally had only 2% sugar left after air-curing and was typically used for chewing tobacco. Since the burley leaf is very spongy and porous, the leaves were soaked in honey, sugar or licorice to sweeten them up and then combine them with the more expensive flue-cured variety, resulting in the ñAmerican blendò.[56]R.J. Reynolds Tobacco Company launched the first ñblendedò cigarette in 1913, the Camel. (Figure 3). Camelôs unique innovation was the result of a combination of the lower pH of flue-cured tobacco, with the higher pH of sweet-flavored burley, resulting in a cigarette that was ñsweet and flavorfulò, as well as ñmild and inhalableò.[57]

The American blend of flue-cured tobacco quickly reached global distribution, and cigarette production in North Carolina became the epicenter of this new ñmilderò combination, controlling roughly half of the American trade.[58] By the 1930ôs, German tobacco scientists were tracing the global lung cancer epidemic to the increasing use of inhalable cigarettes and the correlation to the lower pH of tobacco smoke.[59]Inhalation of cigarettes was encouraged by the cigarette manufacturerôs seductive advertisements (Figures 4 and 5). The tobacco documents library is filled with examples of these advertisements and marketing strategies, as well as the individual tobacco company corporate websites. These cigarette advertisements and growing health concerns initiated the early attempts towards regulation which are discussed in the next section.

Figure 3:

The first Camel cigarette campaign of 1915 announced the arrival of national brands. Designed by the N.W. Ayer Agency to create considerable anticipation and interest of the new American blended cigarette.

(Photo credit: R.J. Reynolds, 1915)

Figure 4:

ñDo You Inhale?ò ï American Tobacco Company advertisement drawn by pinup artist John La Gatta, encouraged cigarette smoke inhalation by associating with sexual satisfaction.

(Photo credit: American Tobacco Company 1932)

Figure 5:

ñDo You Inhale?ò ï American Tobacco Company advertisement drawn by pinup artist John La Gatta, expressed sexual allure of smoking.

(Photo credit: American Tobacco Company 1932)

2.2 HISTORY OF TOBACCO REGULATIONS

The early 1600ôs document the first attempts at tobacco regulation in the North American colonies. In 1619, the first tobacco inspection law was passed by the Virginia House of Burgesses, ordering the lowest grade of tobacco to be destroyed and prohibiting "second growth" tobacco and the marketing of trash leaves.[60] This law was a result of overproduction by colonial tobacco farmers, which had caused a decline in prices as well as the quality of the tobacco leaf produced. In 1621, additional attempts to restrict production required each farmer to limit his growth to 1000 plants of nine leaves each, although this order was rescinded and replaced instead with an act in 1629 that permitted each planter to grow only 3000 tobacco plants.[61]

In 1632, Massachusetts forbid public smoking, and in 1639, Governor Kieft completely banned smoking in New Amsterdam (New York City).[62] In 1647, a colony of Connecticut banned public smoking, declaring that ñcitizens may smoke only once a day, and then not in company with any other," and in 1650, the Colony of Connecticut General Court declared: ñNo smoking by persons under the age of 21, and no smoking except with physicians orderò. [63]

In further attempts to control the problem of overproduction, Carolina, Maryland and Virginia reached a decision to prohibit the planting of tobacco from February 1667 to February 1668, however the wind storms of 1667 almost nearly destroyed the crops that were ready for harvest that year. [64] In 1682, the failure of the Virginia Assembly to pass another tobacco control act led the farmers to take the matter into their own hands by burning both their own crops and the plants of their neighbors.[65] The resulting riot

stimulated legislative action in 1684, making the destruction of tobacco a criminal offense, subject to the death penalty. [66]

The earliest attempts at quality control laws for tobacco were first seen in 1713, when the Virginia House of Burgesses established a warehouse system to enforce tobacco inspection. Forty public warehouses were created, complete with official inspectors.[67] Soon afterwards, tobacco riots ensued when the Maryland Assembly initially refused to follow Virginia's example until Lord Baltimore was convinced that their economic state of affairs would not improve until inspection laws were passed that "will prevent the sending to market such trash as is unfit for any other use but manure".[68] As a result, Maryland followed Virginia in the creation of a tobacco inspection system in 1747, along with Carolina in 1754.

In 1760, Pierre Lorillard established his tobacco company in New York City, which is now the oldest tobacco company in the United States. [69] (The company processed pipe tobacco, cigars and snuff at the time, but now manufacturers two of the top selling cigarettes under its Newport brand. The Lorillard corporate website provides links to its historical documents according to the terms of the Master Settlement Agreement, and provided much insight into the early history of the development of cigarettes).[70]

In 1776, the American Revolution, or ñThe Tobacco Warò, was actually financed by 5 million pounds of Virginia tobacco, which served as collateral for the loan that Benjamin Franklin secured from France.[71] George Washington, who was himself a tobacco farmer, pleaded to his countrymen for aid to the army: "If you can't send money, send tobacco."[72] It was tobacco exports that the fledgling government used to build up credits abroad

during the war, and when the war was over, Americans had to rely on tobacco taxes to help repay the revolutionary war debt.[73]

In 1818, smoking was banned on the streets of Lancaster, Pennsylvania.[74] The first mayor of Lancaster, was John Passmore. Mayor Passmore was one of the first violators of the no smoking ordinance, and he was fined twenty shillings. Passmore was a very stout man, and reportedly weighed 480 pounds. Legend has it that when he died, there was no hearse large enough for him, and his casket was carried in a wagon.[75]

The first organized anti-tobacco movement in the United States began in the 1830ôs as an adjunct to the temperance movement.[76] These antismoking attempts were based upon concerns that smoking caused health as well as social problems, and sought to eliminate tobacco, as well as cigarettes from society.[77] The "Annual Report of the New York Anti-Tobacco Society for 1855", declared that tobacco was a ñfashionable poisonò, and warned against both addiction and the cause of death in half of the smokers aged 35 - 50.[78] The Reverend George Trask preached that tobacco and alcohol were Satan's twins, and ñtobacco is the demon twin of alcohol. Very many of our men and boys are ruined by its power.ò[79] This Temperance antismoking movement culminated in the passage of cigarette prohibition laws in fourteen states in the late 1800ôs and early 1900ôs.[80]

Ironically, it is within this same era that our country had the first federal tax levied on tobacco, in 1862, to help pay for the Civil War, yielding around three million dollars.[81] There was also a federal mandate in 1863 allowing IRS agents to paste Civil War excise tax stamps on cigar boxes.[82] The tobacco taxes had largely stabilized by the 1890ôs, and by that time, they accounted for 31% of total federal tax receipts, or $38.9 million.[83]

By 1890, 26 states and territories had outlawed the sale of cigarettes to minors, although the definition of ñminorò varied between ages 14-24, depending on each particular state.[84] The Anti-smoking reformers petitioned Congress in 1892 to prohibit the manufacture, importation and sale of cigarettes, however the Senate Committee on Epidemic Diseases found that only the individual states had the authority to act.[85] However, there was agreement that cigarettes were a public health hazard, and the committee urged the petitioners to seek redress from state legislatures. The individual states continued their own attempts towards regulating or prohibiting smoking, and in 1893, the state of Washington banned the sale and use of cigarettes, but the law was overturned on constitutional grounds described as ña restraint of free tradeò.[86] In 1898, the Tennessee Supreme Court upheld a total ban on cigarettes by ruling that they are "not legitimate articles of commerce, because they are wholly noxious and deleterious to health. Their use is always harmful."[87]

Tobacco first appeared in the 1890 edition of the *US Pharmacopoeia,* the official government listing of drugs.[88] In 1899, the first edition of the Merck Manual was published, and as an employee of Merck, I was able to secure a copy for the purposes of researching this thesis. Inside, I found several interesting indications for the use of tobacco to treat various ailments ranging from asthma: ñsmoking is sometimes beneficialò, and for nymphomania,ò tobacco so as to cause nausea, effectual but depressing.ò[89] The recommended treatment of constipation was either a tobacco wine or smoking: ñ5 minims of the wine at bedtime or cigarette after breakfast,ò and ñtobacco wine: just short of nauseating, at bedtimeò, was recommended for the treatment of chordee , or penile defect. [90] Tobacco in the form of a poultice was indicated for the

treatment of hemorrhoids, mastitis, and prurigo,(a type of skin irritation), although this indication of tobacco was described as ñuseful but dangerousò.[91]

However, in 1905, "tobacco" did not appear in the US Pharmacopoeia. There was controversy behind its removal from the Pharmacopoeia, and it was alleged to be the price that had to be paid to get the support of tobacco state legislators for the Food and Drug Act of 1906, since the elimination of the word tobacco automatically removed it from FDA oversight.[92] The tobacco companies had threatened that as long as tobacco was included, the tobacco growing states would not support the passage of the 1906 Food and Drug Act, and along with it, the legislation needed to create the Food and Drug Administration.[93]

When the Federal Food and Drug Act of 1906 was ultimately enacted, ñnicotineò was also originally on the list of drugs, until tobacco industry lobbying efforts succeeded in removing it as well as ñtobaccoò.[94] The Federal Food and Drugs Act of 1906, Public Law Number 59-384, 34 Stat. 768, also known as the ñWiley Actò, or the Pure Food and Drug Act, was enacted to prevent the manufacture, sale, or transportation of adulterated or misbranded or poisonous or deleterious foods, drugs, medicines, and liquors, and for regulating traffic therein.[95] This is one of the landmark acts which demonstrated the earliest influence of politics on the regulation of tobacco.

In 1907, the state of Washington passed a law making it illegal to "manufacture, sell, exchange, barter, dispose of or give away any cigarettes, cigarette paper or cigarette wrappers."[96] On January 26th of 1907, under President Teddy Roosevelt, Congress passed the Tillman Act, which prohibited campaign contributions by corporations to candidates

for national posts. However, no restrictions were placed on the individuals who owned or managed the corporations, which made enforcement of the act impossible to achieve.[97] Also in 1907, President Teddy Rooseveltôs Justice Department filed anti-trust charges against the American Tobacco Company according to the Sherman Anti-Trust act of 1890, resulting in the 1911 breakup of the company into fourteen separate companies.[98] From my earlier research into to background and beliefs of Dr. Harvey Wiley, it would be difficult to fathom that he willingly conceded to the withdrawal of tobacco and nicotine from federal oversight. In 1914, the debate over Federal regulation of tobacco continued, with the Bureau of Chemistry in the Department of Agriculture announcement that only tobacco which had been labeled for a medicinal purpose was subject to the scope of the Pure Food and Drugs act of 1906, and that ñtobacco and its preparations which are not so labeled and are used for smoking or chewing or as snuff, and not for medicinal purposes are not subject to the provisions of this act.ò[99]

While Dr. Harvey W. Wiley was the head of the U. S. Bureau of Chemistry, speaking in the Chamber of Commerce in Washington, D. C., at one of the sessions of an annual meeting of the International Reform Bureau, he enumerated as "habit-forming drugs," from worst to least:

ñé é *alcohol, opium, cocaine, tobacco, coffee, tea, chocolate, cocoa. All these are "nervines," that more or less upset the normalcy of the nerves, and make people "nervous" who should be nervy. These nervines so grip the nerves that they demand a new dose with increasing frequency……it is a rascally thing to bind anybody to a habit-forming drug*.ò[100]

In 1927, Dr. Wiley expressed his concerns that the use of any form of tobacco might be harmful and that it might promote cancer.[101]

Even though Dr. Wiley had named tobacco next to alcohol and opium in his list of habit-forming drugs he drew the line in legislation stating,

ñ*The sale of liquors and opium to anybody should be prohibited save as a guarded medicine, but I refused in 1922 to support legislation proposed in Arkansas that carried the prohibition of tobacco beyond minors. I believe we should rely upon argument to stop the use of tobacco in case of adults, whether men or women. But we should by law protect non-smokers against the impositions of selfish smokers who are so careless of the safety and comfort of others that they smoke where they may start a fire, and where they will make others to whom smoke is nauseating or distasteful breathe their second-hand smoke even in places protected by "no smoking" signs."* [102]

Additional quotes by Dr. Wiley,(Appendix D), refer to Hudson Maxim, the inventor of

high explosives for use in battleship guns and torpedoes:

"*The wreath of cigarette smoke which curls about the head of the growing lad holds his brain in an iron grip which prevents it from growing and his mind from developing just as surely as the iron shoe does the foot of the Chinese girl. In the terrible struggle for survival against the deadly cigarette smoke, development and growth are sacrificed by nature, which in the fight for very life itself must yield up every vital luxury such as healthy body growth and growth of brain and mind.*
*If all boys could be made to know that with every breath of cigarette smoke the inhale imbecility and exhale manhood, that they are tapping their arteries as surely and letting their life's blood out as truly as though their veins and arteries were severed, and that the cigarette is a maker of invalids, criminals and fools – not men – it out to deter them some. The yellow finger stain is an emblem of deeper degradation and enslavement than the ball and chain.*ò[103]

After reading Henry Fordôs book, ñ*The Case Against The Little White Slaver*ò, Thomas

Edison sent the following cable to Ford on April 26, 1914:[104]

ñ*Friend Ford,*

The injurious agent in cigarettes comes principally from the burning paper wrapper. The substance thereby formed, is called 'Acrolein'.
It has a violent action on the nerve centers, producing degeneration of the cells of the brain, which is quite rapid among boys.
Unlike most narcotics, this degeneration is permanent and uncontrollable.
I employ no person who smokes cigarettes.

Yours,

Thos A. Edison"

MR. EDISON'S LETTER

Cable Address "Edison New York"

From the Laboratory
of
Thomas A. Edison.

Orange, N.J. April 26 1914

Friend Ford

The injurious agent in Cigarettes comes principally from the burning paper wrapper. The substance thereby formed is called "Acrolein".
It has a vident action on the nerve-centers, producing degeneration of the cells of the brain, which is quite rapid among boys.
Unlike most narcotics this degeneration is permanent and uncontrollable.
I employ no person who smokes Cigarettes.

Yours
Thos A Edison

In 1929, the lack of Federal jurisdiction of tobacco was addressed again, when legislation was introduced with the intent of placing tobacco within the regulatory jurisdiction of the Bureau of Chemistry, since it was charged with enforcing the nationôs drug laws. [105] However, in reviewing the earlier provision which noted that the Bureau of Chemistry had no jurisdiction over tobacco which was not labeled as medicinal, Congress did not pass the bill.

The Bureau of Chemistry was no longer the regulator of drugs once the Federal Food, Drug, and Cosmetic Act was enacted in 1938, which resulted in the creation of the FDA. Under the FDCA, the FDA was granted jurisdiction over any drugs intended to affect the structure or any function of the body, as well as any device which was intended to deliver such a drug into the body. [106] Similar to the Bureau of Chemistry, the FDA also announced that it had no jurisdiction under the FDCA over any tobacco product as a drug, unless there was a claim that it was being sold for a medicinal purposes by the manufacturer, a position that was reiterated between 1940 and 1952.[107]

In 1956, a bill was introduced to amend the FDCA in order to grant the FDA regulatory authority over cigarettes, however, this bill did not pass.[108] The first real assertion of FDA authority over tobacco products occurred in 1959, when the Federal Drug Administration claimed authority only because the Fairfax Cigarette company had advertised that their cigarettes would reduce body weight.[109] Leaflets seized with the cigarettes also described a ñmiracle vaporò that could reduce the frequency of respiratory diseases, in which the FDA determined fell within the statutory definition of ñdrugò.[110] In 1963, bills were introduced in both the House and the Senate to place all smoking products under the authority of the FDA. [111] The sponsor of this proposed House bill

acknowledged that the reason for the bill was that "smoking products do not come under the protection of the FDA", and similarly to all previous attempts, neither of these bills passed.[112]

Because of mounting evidence confirming Dr. Wiley's early warnings, Good Housekeeping magazine stopped accepting cigarette ads in 1952, 12 years before the U.S. Surgeon General issued a report in 1964, detailing the health hazards of smoking. [113] This landmark turning point in tobacco regulation occurred on January 11th, 1964, when Surgeon General Luther L. Terry, M.D., released the first report of the Surgeon Generalôs Advisory Committee on Smoking and Health.[114] The release of this report was the first series of steps to diminish the impact of tobacco use, and it outlined the health risks associated with smoking and tobacco use. Legislation was again introduced seeking to grant the FDA the authority to regulate tobacco and cigarettes as a result of the Surgeon Generalôs Report. [115] However, this time, in a hearing before the House Committee on Interstate and Foreign Commerce, officers from both the Department of Health, Education, and Welfare (HEW) as well as the FDA, testified that the FDA had no jurisdiction to regulate tobacco under the FDCA without a claim of medicinal purpose.[116] Rather than granting the authority to regulate tobacco to the FDA, Congress ultimately enacted the Federal Cigarette Labeling and Advertising Act of 1965 (FCLAA), in order to establish a comprehensive Federal program to deal with labeling and advertising and the relationship between smoking and health.[117] Over the thirty years since the enactment of the FCLAA, several attempts to place tobacco under the regulatory authority of the FDA were introduced in Congress, none of them passed, and the FDA was not legislatively granted jurisdiction over tobacco and tobacco products.

The FDA Commissioner Charles Edwards, reaffirmed that the FDA did not have jurisdiction over tobacco in a 1972 Congressional hearing, stating that "the regulation of cigarettes is to be the domain of Congress, and labeling or banning cigarettes is a step that can be taken only by the Congress. Any such move by the FDA would be inconsistent with the clear congressional intent."[118] Commissioner Edwards had testified that cigarettes would qualify as drugs only if tobacco companies marketed them by reference to their beneficial effects on the human body. The FDA also rejected a plan by the General Counsel of HEW, Wilmont Hastings, to initiate a test case in order to determine whether the FDA had jurisdiction over cigarettes. [119]

Congress enacted the Toxic Substances Control Act (TSCA) in 1976, empowering the EPA to regulate substances that might pose a threat to health, however, the TSCA's definition of chemical substance included an exception for "tobacco or any tobacco product." [120] That same year, following a district court ruling which granted the Consumer Product Safety Commission jurisdiction to consider a petition to regulate cigarettes under the Federal Hazardous Substances Act (FHSA), Congress amended the FHSA to exclude tobacco and tobacco products from its definition of a hazardous substance.[121] In doing so, Congress stated that, ñthe clear mandate of Congress is that the basic regulation of tobacco and tobacco products is governed by the legislation dealing with the subject, the Cigarette Labeling and Advertising Act of 1965, and that any further regulation in this sensitive and complex area must be reserved for specific Congressional action.ò [122]

The debate between the FDA and Congress over the jurisdiction of tobacco continued from 1977 until 1979, culminating in five bills being introduced into Congress.

Unfortunately, Congress clearly stated its intent that it alone should be the sole Federal regulator of tobacco and tobacco products by failing to pass any of these. [123]

Up until this time, most of the attempts to place tobacco within the regulatory reach of the FDA had come from Congress itself. However there were external attempts at petitioning the FDA to assert jurisdiction over tobacco.

On May 26, 1977, Action on Smoking and Health, (ASH), in conjunction with thirteen other organizations and individuals, filed a citizen petition with the Food and Drug Administration requesting: (1) that the agency assert jurisdiction over cigarettes containing nicotine as a "drug" or a "device"; (2) that the agency regulate cigarettes no less strictly than saccharin; and (3) that the agency restrict the sale of cigarettes to pharmacies. ASH contended that section 201(g)(1) (C) of the Food, Drug, and Cosmetic Act provided the agency with the requisite jurisdiction over cigarettes as a drug. In a letter memorandum dated December 5, 1977, however, the Commissioner of Food and Drugs, Donald Kennedy, rejected ASH's contention. The Commissioner based his rejection upon the agency's consistent position that cigarettes will not be deemed a drug unless health claims were made by the cigarette vendors. The Commissioner noted that he would respond to ASH's request that the FDA assert jurisdiction over cigarettes as a device in connection with ASH's planned separate petition.[124] ASH filed suit in order to challenge that decision, with the chief issue in this case being ASH's contention that tobacco manufacturers were selling cigarettes with the sole intention of delivering a body altering drug, (nicotine), placing them within the regulatory jurisdiction of the FDA.[125] Unfortunately, the Circuit Court affirmed the lower court's holding that ASH did not establish the near exclusivity of consumer use of cigarettes with the intent to affect the

structure or any function of the body of man. In holding that tobacco did not fall within the regulatory jurisdiction of the FDA, the Circuit Court concluded that any expansion of the FDCA remained the responsibility of Congress.[126] Tobacco regulation continued to be addressed by Congress almost annually since the ASH petition, however, there was nothing significant to indicate any change in Congress' approach towards FDA regulation of tobacco and tobacco products. The ASH citizenôs watchdog group continued its anti-tobacco crusade, and is still active, maintains a website, blog and an office in Washington D.C.[127] In 1984, the House Committee on Energy and Commerce stated that "Federal laws that protect the public from hazardous food, drugs, and consumer products do not apply to cigarettesò, once again reaffirming Congress' stance that tobacco and tobacco products do not fall within the regulatory reach of the FDA.[128] In 1987, 1989, 1992, and 1993, bills were introduced to create new regulatory categories for tobacco and tobacco products to place them under the regulatory scope of the FDA.[129] Unfortunately, none of these bills were enacted either.

By the end of the 1980ôs, the bulk of congressional regulation of tobacco and tobacco products rested on just two statutes: The Federal Cigarette Labeling and Advertising Act (FCLAA) of 1965, and the Comprehensive Smokeless Tobacco Health Education Act (CSTHEA) of 1986. Both statutes regulated the manufacture, packaging, and distribution of tobacco and tobacco products, and also granted the Department of Health and Human Services (HHS) the authority to review lists of ingredients added to the tobacco, and to report to Congress on any perceived health effects of any added ingredients.[130] Although the Federal Cigarette Labeling and Advertising Act (FCLAA) requires manufacturers to provide a list of cigarette ingredients to the Secretary of the Department of Health and Human Services (HHS), these lists are neither brand nor company specific, rather, the

industry, constructed a single list of ingredients based on overall volume and usage. After receiving each tobacco companyôs complete, non-branded list of all ingredients used in cigarettes, a ñmasterò list consolidated these individual lists and listed the ingredients by weight. This master list is then sent to HHS but is neither company nor brand specific, because the FCLAA treats the information in these lists as ñtrade secret or confidential.ò[131] Additionally, the federal government was not the only regulator of tobacco and tobacco products during this time frame. There were also state government restrictions in place throughout all fifty states including restrictions on tobacco and tobacco products use by minors, licensing requirements, and restrictions on vending machine and loose cigarette sales.[132] The states and localities had placed a variety of restrictions on smoking in sites such as workplaces, restaurants, and public transportation by the end of 1980ôs.[133] A number of additional ordinances were in place at the county and local levels, and many sites had voluntarily become smoke-free as well by this time frame.

The overall viewpoint of the FDA consistently maintained through the years 1963 and 1988, was that tobacco products did not otherwise qualify as drugs, devices, foods, or cosmetics.[134] Cigarettes would be counted as drugs if, and only if, claims about beneficial physical effects were made on their behalf, or in other words, cigarettes would qualify as drugs only if tobacco companies marketed them by reference to their beneficial effects on the human body. In 1988, the American Heart Association petitioned the FDA to regulate low-tar cigarettes as drugs. The FDA responded by announcing its intention to reconsider the jurisdiction over cigarettes and smokeless tobacco, a position that was ultimately revealed in 1996, with the Proposed Rule by FDA Commissioner, David Kessler.[135]

CHAPTER 3

DR. DAVID KESSLER

3.1 A QUESTION OF INTENT

By the time Dr. David Kessler took the reins as Commissioner of the FDA in 1990, Congress had for the past sixty years clearly demonstrated that it should be the sole federal regulator of tobacco and tobacco products. A comprehensive federal program had been implemented by Congress to regulate tobacco and tobacco products, and this program included regulation by the FDCA, FCLAA, CSTHEA, as well as several other Government Agencies. Furthermore, this federal program had been supplemented by various regulations in all fifty states. Although these regulations appeared to adequately regulate the manufacture, packaging, marketing, distribution and sales of tobacco and tobacco products, the fact remained that cigarettes continued to be the nationôs number-one killer.[136] Dr. David Kesslerôs book, *A Question of Intent*: *A Great American Battle With a Deadly Industry*, published in 2001, summarizes his account of the FDAôs decision to take on tobacco and its search for evidence to support its jurisdictional claims.[137]

David Kessler claims that he did not intend to regulate smoking when he became the Commissioner of the FDA in 1990. Rather, the impetus came from Jeff Nesbitt, a former aide of Dan Quayle, who first suggested that Kessler ñtake-onò tobacco.[138] Additionally, further impetus came from a petition submitted to the FDA from the Coalition on Smoking and Health, which asked for FDA regulation of tobacco. In an Agency letter

responding to the coalitionôs petition, Kessler opened the door to possible regulation when he indicated that there was some evidence suggesting that cigarette companies intend the obvious ï that consumers buy cigarettes to ñsatisfy their nicotine addictionò.[139] The letter noted that the FDA would have a legal basis to regulate tobacco products as drugs, if it could compile an adequate record.[140] At that time, the FDA had just emerged from the Reagan era severely underfunded, and under constant OMB pressure to deregulate. Kessler admits in the book that he had a steep learning curve, and that there were difficulties in acquiring information about the tobacco industry. Kesslerôs staff choices for the investigation were non-traditional FDA inspectors from various backgrounds including the Secret Service and the FBI.[141] The investigation involved confidential interviews with tobacco industry informants, who were given code names like, ñDeep Coughò or ñResearchò. Deep Cough was one of the most important sources of industry information that the FDA had questioned, as he had provided strong evidence of tobacco companies fortifying their products through the addition of nicotine. This fortification theory was important to the FDAôs case, since proof of a deliberate addition of an addictive substance would have established that the cigarette manufacturers intended that tobacco functioned as a drug. Unfortunately, soon after talking with the FDA, Deep Cough appeared on an ABC *Day One* television broadcast, accusing tobacco companies of fortifying their products through the addition of nicotine, and Philip Morris subsequently sued the television station for libel.[142] As a result, Dr. Kessler was forced to launch an intensive effort to gather additional evidence showing that cigarette manufacturers intended that tobacco function as a drug. The FDAôs subsequent investigation into the cigarette manufacturersô production and distribution processes

demonstrated the difficulty involved in acquiring information about the tobacco industry and the lack of adequate regulatory authority. To assert regulatory over tobacco, the FDA needed to prove that tobacco met the statutory definition of drug: an article ñintendedò to prevent or treat disease, or ñ intended to affect the structure or any function of the body.ò [143] This intent is ordinarily established by express claims attributable to the manufacturer in the productôs labeling, in advertising, or in other relevant materials.[144] These direct expressions are not the only means for establishing intent, because a finding of intent can also rest upon external factors, and specifically to Dr. Kesslerôs case, this was establishing the intent of consumer use.[145] Under the consumer use approach, a substance is said to satisfy the intent requirement as long as consumers use the substance as a drug, and manufacturers can reasonably foresee that consumers will use the substance with this same intent. However, the FDA had historically been unsuccessful in adequately establishing consumer use in actual practice without much difficulty.[146] The FDAôs decision in the ASH case which I mentioned earlier in this thesis, did leave open the possibility that intent could be established through consumer use, even in the absence of express claims by the manufacturer, however, with the caveat: ñConsumer use needs to occur predominantly and in fact nearly exclusively with the appropriate intent.ò[147] Additionally, both the FDA and the cigarette manufacturers had historically claimed that consumers smoke tobacco merely for ñ pleasure,ò and thus that mere smoking provided in itself a negative answer to the question of intent.[148] As a result, Dr. Kessler reopened the consumer use approach and needed to demonstrate manufacturer intent in the absence of express manufacturer claims. Dr. Kesslerôs team of investigators assembled an impressive record of numerous scientific studies to support its jurisdictional claim.

These scientific studies provided the evidence to show that tobacco does not merely provide ñsmoking pleasure,ò but also adversely affects the body and brain in ways that cause and sustain addiction.[149] Since it was conceivable that a manufacturer would realize that tobaccoôs addictive properties motivated consumer use at least in part, Dr. Kessler and his team of investigators took the position of the question of intent.[150]The key to identifying the legal language that could be used to affirm the FDAôs case was supplied by David Adams, a lawyer from the FDAôs policy office. Adams told Dr. Kessler that instead of regulating tobacco, the agency should regulate its active ingredient, nicotine: ñCigarette manufacturers can take the nicotine out, but they leave it in. That goes to the question of intent.ò[151] That could bring nicotine within the FDA statute of regulation.

3.2 TOBACCO DOCUMENTS ARE THE SMOKING GUNS

Dr Kessler and his team of investigators supported the FDAôs question of intent argument with internal industry documents which indicated that the cigarette manufacturers understood tobaccoôs addictive effects, and with the evidence that suggested that the industry was well aware of these addictive effects when designing and manufacturing their products.[152]

The FDA relied heavily upon a collection of Brown & Williamson Tobacco Company internal documents which had been pilfered by a paralegal working for a product liability law firm that was representing the company.[153] The paralegal, a smoker of B & W cigarettes for 30 years, had sought to use the papers in a personal injury suit against the company following his emergency triple bypass surgery. The paralegalôs attorney advised against using the papers, cautioning that copying of the papers would violate the B & W attorney-client privilege. Philip Hilts, the lead tobacco reporter for the *New York Times*

obtained these documents from a congressional source to whom they were leaked and published a story based on them.[154] The FDA was able to access the B&W documents through the same confidential congressional source.[155] The significance of these documents to provide evidence in support of the FDAôs position is acutely illustrated by a quote from one of the documents, which is a memorandum from Addison Yeaman, the companyôs general counsel in 1963: ñWe are, then, in the business of selling nicotine, an addictive drug . . . .ò [156]

In a memorandum by Claude Teague, an R. J. Reynoldôs Tobacco Company executive, there was evidence that the tobacco companies were aware of nicotineôs addictive nature and of the role that addiction plays in consumer use:

ñNicotine is known to be a habit-forming alkaloid. . . .Thus, a tobacco product is, in essence, a vehicle for delivery of nicotine. . . .If . . . nicotine is the sine qua non of smoking, and if we meekly accept the allegations of our critics and move toward reduction or elimination of nicotine from our products, then we shall eventually liquidate our business. . . .Tobacco products uniquely contain and deliver nicotine, a potent drug with a variety of physiological effects.ò [157]

These internal tobacco documents also assisted litigation efforts on behalf of Mike Moore, the Mississippi Attorney General, in order to recover smoking-related Medicaid costs and the eventual Master Settlement Agreement (MSA).[158]

As a result of the investigation, Dr. Kessler was able to identify specific manufacturing methods that artificially enhanced the impact of nicotine by the addition of ammonia, which when added to tobacco, òliberates free nicotineò, and this produced a smoke that was also richer in nicotine.[159] The FDA also discovered that variations of tobacco plant

types contained different proportions of nicotine, which meant that the manufacturers could control the nicotine levels in their products through blending.[160] An FDA laboratory was able to determine that the nicotine levels within each brand of cigarettes possessed a uniformity similar to when measuring the consistency of active ingredient levels in pharmaceutical drug manufacturing.[161] Tobacco manufacturers had consistently maintained that the nicotine level in tobacco occurred at a 1:15 ratio of nicotine to tar, and this was their defense used when charged with nicotine manipulation.[162] However, Dr. Kessler discovered that the ratio of nicotine to tar in the lowest tar cigarette was 1:10, which demonstrated that the concentrations of nicotine and tar varied inversely.[163] Dr. Kessler also discovered that with progressive tar reductions, cigarette manufacturers took steps to boost nicotine concentrations to the pharmacologically active levels of around 0.5 to 0.8 mg per cigarette.[164] There were additional investigations documenting B&W's experimental genetic manipulation of a high nicotine plant, Y-1 in South America, and evidence that some of the genetically modified tobacco had already been used in cigarettes sold in the United States.[165]

Ultimately, the FDA's efforts under Kessler's direction demonstrated that a cigarette is a device, designed to deliver controlled amounts of the drug, nicotine throughout the body. Additionally, the evidence that nicotine in tobacco had an addictive effect, and that the tobacco companies manufactured and designed cigarettes with the intention of delivering nicotine's addictive effect, were evidence enough to support the position that cigarettes were a combination drug and device, subject to the jurisdiction of the FDA.

However, the FDA took the approach at directing its regulatory efforts against youth smoking, proposing that the rule restricted the accessibility, promotion, and labeling of

tobacco products to kids under the age of eighteen, and required that retailers verified the age of all purchasers younger than twenty-seven through the use of photo identification, and placed adult-only location limitations on cigarette vending machines, as well as restrictions in advertising and print.[166] The regulation would also require the tobacco industry to spend $150 million each year to support prevention education of children, and also banned promotional items, free cigarette samples, color advertisements in magazines targeted at youth under the age of 18, as well as banned advertisement and sponsorship of sporting or entertainment events.[167]Dr. Kesslerôs position on tobacco use in youths was derived from the research uncovered during the investigation that provided evidence that the cigarette manufacturers knew that most smokers become habitual users before the age of eighteen, and those who did not smoke as an adolescent were unlikely to begin smoking later.[168]

Unfortunately, Dr. Kesslerôs Proposed Rule was challenged immediately in both Halls of Congress and the tobacco states of the South, including lawsuits filed by the five largest tobacco manufacturers in the United States, joined by retailers, advertisers and tobacco farmers. There was also the introduction of Congressional legislation in order to pre-empt or prohibit outright, the FDA regulations.[169]However, President Bill Clinton approved the Proposed Rule on August 23, 1996 on the advice of his consultant, Dick Morris, who saw the rule as an opportunity for the President to gain momentum against the Republican Congress, boosting his prospects at reelection.[170]Unfortunately, the lower courts largely invalidated the Proposed Rule by concluding that the FDA did not have the authority it claimed under existing statutes. And after appeals, the U.S. Supreme Court affirmed by a 5-4 vote, the lower decision against the FDA. On March 21, 2000,

although acknowledging the harm of cigarette use in minors, the Supreme Court majority agreed that Congress did not intend to give the FDA regulatory control over tobacco.[171] Dr. Kessler wrote, ñThe decision that could have saved hundreds of thousands of lives has been lost by a single vote.ò[172]Dr. Kessler wrote that Justice Sandra Day OôConnorôs tone had been somber as she summarized the majorityôs opinion, explicitly acknowledging smoking as ñone of the most troubling public health problems facing our nation todayò, and that the Agency had ñamply demonstrated that tobacco use, particularly among children and adolescents, poses perhaps the single most significant threat to public health in the United States.ò [173] The Tobacco Legacy Documents online website is full of evidence supporting Dr. Kesslerôs Proposed Rule, including: evidence of addiction, nicotine manipulation and the targeting of youth by tobacco companies. For example, one of Dr. Kesslerôs investigators located a sales memo from Reynolds Tobacco Company instructing the local sales representatives to identify accounts near high schools and college campuses.[174] By searching the word, ñyoungò, I found a quote from the Winston Man model, David Goerlitz, who claimed that when he asked a tobacco executive if he could take home the cigarettes from a photo shoot, and whether or not any of the tobacco executives smoke, the Reynolds tobacco executive said, ñAre you kidding? We reserve that right for the poor, the young, the black and the stupid.ò Goerlitz was also told that his job was to be a ñlive version of a G.I. Joe action figureò, and ñto help the industry get four thousand kids per day to start smoking.ò[175] In a 1973 memo by Claude Teague, the RJ Reynolds assistant director of research, he states,òRealistically, if our company is to survive and prosper, over the long term, we must get our share of the youth market.ò[176]In a 1975 Reynolds memo stamped, òSecretò, an update is given on the

ñMeet the Turkò campaign, concluding that, òTo ensure increased and longer-term growth for the Camel Filter, the brand must increase its share penetration among the 14-24 age group which have a new set of more liberal values and which represent tomorrowôs cigarette business.ò[177] The 14-24 age youth market is also described as, ònew startersò, and ñreplacement smokersò, in another internal memo, with sinister implications that the cigarette companies were well aware that it was important to get kids addicted early in order to grow their business long term.[178] Dr. Kessler also indicated that had the rule survived, the Agency would have considered additional restrictions going beyond teen smoking, such as the possibility of ñreducing the level of nicotine in cigarettes over time, with an eye toward eventually weaning smokers from the addictive agent.ò[179] This concept is revisited again, within my thesis discussion pertaining to the passage of President Obamaôs Tobacco Control Act of 2009, and is also included in the transcript of my interview teleconference with Dr. David Kessler on November, 12th, 2012.

3.3 TELECONFERENCE INTERVIEW

In preparing the list of potential questions to ask Dr. Kessler during the interview, the most logical place to start was with his book, ñA Question of Intentò. Additionally, a 1998 PBS Frontline Interview online transcript provided the basis for developing a unique list of core questions, while also avoiding possible duplications.[180] In both his book, as well as the Frontline interview, Dr. Kessler had questioned whether our country was going to ñbreak the hold that the tobacco industry has on our elected representativesò, and whether ñfor the first time in a half century, the real power of the tobacco industry over the Congress is going to change.ò[181] It was important to ask a series

of questions that would provide both a status check of these issues that Dr. Kessler had raised back in 1998, along with his thoughts on the 2009 FSPTC Act provisions. The following questions were developed with the goal of balancing Dr. Kesslerôs historical perspective along with his current thoughts on present FDA regulatory efforts, as recorded in the final interview teleconference transcript (Appendix E):

1) What does FDA control of tobacco really mean, and how far have we come?
2) Outside of complete prohibition, what else does the FDA need to do in order to reduce the healthcare burden of tobacco?
3) What will be the impact of new regulations which now permit the FDA to inspect tobacco manufacturing facilities since they havenôt historically followed and GMP, CAPA or Quality Systems regulations?
4) What should the FDA expect from these inspections, i.e., product recalls, seizure, fines?
5) What design modifications should the FDA require so that cigarettes are safer?
6) How difficult would it be for the FDA to implement an industry wide reduction in nicotine levels?
7) How can a national healthcare policy continue to support the funding of tobacco related diseases?
8) What was the most significant result of the MSA Tobacco Documents online repository?
9) What regulatory changes would you suggest if you had the opportunity to work again with the FDA?

The interview allowed me to speak directly to the author of one of the most fascinating books written on the subject of the tobacco industry and FDA regulations, during his tenure as FDA Commissioner. The resulting interview addressed the context of the proposed questions, and there were some key highlights which supported the validation of my earlier research efforts. Dr. Kessler maintained a constant theme throughout the interview, in that the current FSPTC Act is ñevolvingò, and that although the FDA does now have the jurisdiction that it needs, it may take ñdecadesò for the FDA to learn what it needs to do to fully regulate tobacco. When asked about GMP of tobacco manufacturing companies, and what that means for the FDA when attempting an inspection, Dr. Kessler admitted that unlike what is seen in traditional Pharmaceutical companies and GMP, the tobacco industry ñknows much more about their quality than the FDA does, and it will take decades to learn.ò Similarly to the chapters within his book, Dr. Kessler admitted that the cigarette is ña highly engineered productò, and that although nicotine levels cannot be reduced to zero, ñyou can do an essenceé a set level that nicotine can be reduced toé .it needs to happen.ò Dr. Kessler provided additional comments to supplement research findings on nicotineôs implications in diabetes, stating that ñmany areas are still unexplained. I donôt think we fully understand the full effect of nicotineò. Overall, the interview provided a regulatory perspective as well as the scientific and social rationale of both historical and present FDA policy decision making. Most importantly, Dr. Kessler provided a realistic expectation of the timeline needed to fully implement FDA authority under the FCPTC Act.

CHAPTER 4

POLITICAL INFLUENCES OF FDA TOBACCO REGULATIONS

4.1 TOBACCO CONTROL ACT OF 2009

Following the 2000 Supreme Court decision final ruling that the FDA did not have jurisdiction over tobacco products, the issue was sent back to Congress for further consideration, where it remained idle until 2008. The House of Representatives voiced support for a new tobacco act, H.R.1108, which former President George W. Bush threatened to veto, even after it had passed with 98% of the Democrats support.[182]There had been large opposition to the law from the 110th Congress, especially from the tobacco states such as North Carolina. The Family Smoking Prevention and Tobacco Control Act (also known as the FSPTC Act) was finally signed into law by President Barack Obama on June 22, 2009. [183] The Family Smoking Prevention and Tobacco Control Act gives the FDA explicit regulatory authority over tobacco products to protect and promote the health of the American public. Among other things, this historic legislation gives the agency the authority to require companies to reveal all of the ingredients in tobacco products, including the amount of nicotine, and to prohibit the sale of tobacco products labeled as ñlight,ò ñmild,ò or ñlow.ò Further, with this new regulatory mandate, FDA will regulate tobacco advertising and require manufacturers to use more effective warning labels, as well as restrict the access of young people to their products. FDA will also assess and regulate modified risk products, taking into account the impact that their availability and marketing has on initiation and cessation of tobacco use. This

bill changed the scope of tobacco policy in the United States by finally giving the FDA the ability to regulate tobacco products, similar to how it has regulated food and pharmaceuticals since the passing of the Pure Food and Drug Act in 1906. The act spans eighty-four pages in its final edition, and gives the FDA comprehensive control on US tobacco products, specifically cigarettes and/or smokeless tobacco. Two months later, on August 19th, 2009, the FDA launched the new Center for Tobacco Products, located on the FDAôs White Oak Campus in Silver Spring, Maryland.[184] The main duties of the Center for Tobacco Control are as follows:

- Set performance standards.
- Review applications for new and modified risk tobacco products before they reach the market.
- Require and control warning labels.
- Establish and enforce advertising restrictions.

The FSPTC Act also called for the creation of a Tobacco Products Scientific Advisory Committee (TPSAC), which met for the first time on March 30th, 2010.[185] The main purpose of the TPSAC is to assess health and safety issues concerning tobacco products, and then to provide advice, information or recommendations to the Commissioner of the FDA based on their findings. Specifically, the TPSAC will submit reports on:

- The impact of the use of menthol in cigarettes on the public health, including such use among children, African Americans, Hispanics and other racial and ethnic minorities.

- The nature and impact of the use of dissolvable tobacco products on the public health, including such use on children.
- The effects of the alteration of nicotine yields from tobacco products and whether there is a threshold level below which nicotine yields do not produce dependence on the tobacco product involved.
- Any application submitted by a manufacturer for a modified risk tobacco product.

The TPSAC committee consists of 12 members serving four-year terms, with expertise in the field of medicine, science, or technology involving tobacco products. The 9 voting members are all representative of the health care professions relevant to tobacco use such as pulmonology, cardiology or toxicology. The three non-voting members include representatives from the tobacco manufacturing industry.[186] On March 19, 2010, the FDA issued a set of regulations concerning tobacco use in kids and adolescents, as required in the FSPTCA, with the intent of decreasing the appeal and accessibility of tobacco products to kids and adolescents, along with rules concerning the sales, distribution and marketing of tobacco products as well as marketing. Several of these were part of the Proposed Rule that Dr. Kessler had first proposed in 1996, in particular, these new regulations under the FSPTCA were created with the intent of decreasing the appeal and accessibility of tobacco products to kids and adolescents. These new rules include:

- Illegal for cigarettes or smokeless tobacco to be sold to anyone under 18.
- Prohibiting the sale of cigarette packages with fewer than 20 cigarettes in them.

- Not allowing cigarettes or smokeless tobacco to be sold in any "impersonal mode of sale (i.e in a vending machine or self-service display).
- Prohibiting free samples of cigarettes or smokeless tobacco.
- Prohibiting tobacco brand name products to sponsor social, cultural, athletic, or musical events.
- Prohibiting gifts in return for the purchase of cigarettes or smokeless tobacco.
- Prohibiting the distribution (or sale) of any items with tobacco logos or brand names.
- Requiring that audio ads have no music or sound effects, only words.

This set of regulations covered cigarettes and smokeless tobacco, but not cigars, pipes or hookah tobacco. Pre-existing state laws that are were not covered by these regulations, or were more stringent than these regulations (such as making 19 the minimum age to purchase tobacco), were to remain in effect. Enforcement of these regulations was through inspections by FDA employees and FDA commissioned state employees. These rules became effective on June 22, 2010, and the five big tobacco companies immediately responded with a civil lawsuit against the United States and the FDA.[187]The tobacco companies argued that the increased size of warning labels and new restrictions on packaging design as well as the ban on publicizing relative risk claims, all interfered with their First Amendment rights to communicate with adult consumers of their products. On January 4th, 2010, Judge H. McKinley, Jr. issued his Opinion of the Court ruling largely in favor of the United States and the FDA on all counts with the exception of a full ban of graphics and colors on advertisements and packaging, which the judge felt would infringe on the First Amendment rights of tobacco companies.[188] However, the FSPTC Act was

not entirely a disappointment to the largest tobacco companies, especially for Altria, the parent company of Philip Morris, the producer with the greatest market share. [189] The FSPTC Act effectively solidified their 50% market share, because of the new stringent advertising regulations banning sponsorship of sports, entertainment events, color or photo ads in publications with significant teen readership, and free gifts with tobacco products. These new restrictions will decrease the competitorôs chances of bringing a new product to market, as well as reduce the competitor companiesô ability to advertise their products, and consequently less ability to convince consumers to switch to their products. However, there is a downside for Philip Morris in that all companies will now be taxed in proportion to their market share, and these funds are going to be used towards the tobacco regulations.[190] ñBringing new products to market will be extremely difficult,ò says Maura Payne, a spokeswoman for Reynolds America, which owns R.J. Reynolds, the manufacturer of Camel, Winston, Doral among several other brands.[191]The FSPTC is built around a public health standard that represents a drastic departure from the traditional ñsafety and efficacyò standard in the Food, Drug and Cosmetic Act, which has historically been the source of regulatory angst in previous attempts towards FDA jurisdiction. Instead, the FSPTC Act obligates the FDA to regulate tobacco products in a manner that is ñappropriate for the protection of public health.ò [192]Indeed, within the 84 pages of the FSPTC Act and on the new Center for Tobacco Control FDA website are additional regulations to market a new tobacco product in the United States.[193] Firstly, a written order must be received from the FDA permitting the marketing of the new tobacco product under one of the following three pathways:

- A Substantial Equivalence Report

- An Exemption from Substantial Equivalence Request
- A Premarket Tobacco Application

However, since the 2009 passing of the FSPTC Act, the FDA has taken little to no action on pending applications.[194]In response to a Freedom of Information Act request by Dr. Greg Connolly, who was a former member TPSAC, and is a professor from the Harvard School of Public Health, there were at least 3293 pending industry applications for substantial equivalence determinations by the FDA as of April 2012.[195] The same Freedom of Information Act response revealed that there has not been one tobacco company file a single new product application, which indicates that the overall strategy is to bring all new products to market by using the substantial equivalence short-cut.[196]This assertion implies that these new products are the same, or present no different public health issues than currently marketed tobacco products. The FSPTC Act also mandates the public disclosure of applications for modified risk tobacco products, and to date, none of these applications have been publically disclosed.[197]In order to make a modified risk claim about a tobacco product, a Modified Risk Tobacco Product Application must be submitted and an order must be obtained from the FDA permitting the marketing of a modified risk product. This application is needed when the productôs label, labeling, or advertising say explicitly or implicitly that the tobacco product:

- Is less harmful than another tobacco product
- Has a lower risk of tobacco-related disease than another tobacco product
- (or its smoke) does not contain or is free of a substance
- (or its smoke) contains a reduced level of a substance

- (or its smoke) presents a reduced exposure to a substance

It is also necessary to submit this type of application and obtain an order from FDA permitting marketing before using any descriptors, and prohibits those descriptors such as ñlightô or ñlow tarò.[198] This modified risk premarket application process would allow for regulatory scrutiny prior to a product being introduced to the market, and prior to consumer use. However, a potential weakness of this approach is that presently, nothing is required of manufacturers claiming substantial equivalence to products already on the market, which is both a financial and time disincentive to produce new reduced risk products.[199]

The real opportunity for the FDA to make an impact on public health lay in SECTION 3, items subparts(3)and (5) of the FSPTC Act, where now the FDA can set manufacturing control standards as well as regulate the levels of tar, nicotine and harmful components, which are all reflective of Dr. Kesslerôs earlier efforts to regulate tobacco.[200] However, there are limitations built into the FSPTC Act which prevent a complete reduction of nicotine levels or a complete ban of tobacco products, and the FDA has yet to issue mandatory product standards that would limit the allowable levels of harmful ingredients in finished tobacco products and smoke.[201] There is much controversy behind the FSPTC Act provisions which prevent the restricting of nicotine levels to zero, and the ñstay of executionò which has been given to menthol as an additive. The FSPTC Act section 907(e) mandated that the new Tobacco Products Scientific Advisory Committee (TPSAC) developed a report and provided recommendations that address the issue of the impact of the use of menthol in cigarettes

on the public health including such use among children, African-Americans, Hispanics, and other racial and ethnic minorities.[202] The TPSAC was mandated to complete its report and recommendations on menthol in cigarettes within one year of its establishment, that is, by March 23, 2011. This report addressed the use of menthol in cigarettes as called for by the Act, with the goal of providing the evidence related to any public health impact of the use of menthol in cigarettes and to offer evidence based recommendations to the FDA. This was the first report prepared by TPSAC, it also described the principles and practices by which TPSAC developed the report, offering a precedent that will be followed, as appropriate, for future reports. The methods that the TPSAC used in developing this report, included evidence from diverse sources including literature searches from Pub Med as well as the Legacy Tobacco Documents online database searches via FDA contractors and relevant articles supplied to the Menthol Subcommittee by the tobacco industry and the public. [203] The TPSAC concluded in their report to the FDA thatò the availability of menthol cigarettes has an adverse impact on public health by increasing the number of smokers with resulting premature death and avoidable mortality, and there is sufficient evidence to conclude that the availability and marketing of menthol cigarettes increases the prevalence of smoking in the general population and particularly in African-Americans and youth, but the evidence is insufficient for Hawaiians/Pacific Islanders and women.ò[204]Currently, the FDA has not taken any action towards menthol products other than the announcement over a year ago pertaining to a second, completely discretionary review of the scientific evidence. Appendix B at the end of this thesis provides a timeline of the FDA Tobacco Law and Menthol Provisions, and a review of the FDA Center for Tobacco Products website for

upcoming meeting and conference agendaôs do not list menthol as a topic of discussion.[205] As a result of the TPSAC report, the FDA recommendations could require a ban on menthol cigarettes, regulation of menthol levels, regulation of menthol cigarette marketing, or require further studies consistent with the scientific findings of the report. However, the delay in any action by the FDA has demonstrated to some tobacco control experts that ï ñthe menthol issue is not a scientific one, but purely a political and policy one.ò[206] In an editorial published by Reuters.com, Paul Smalera called out Congressional Black Caucus members who, despite their stand against disproportionate marketing of mentholated cigarettes to African Americans prior to the FSPTC Act, still supported the law once Philip Morrisôparent company had ñdonated more than $1.5 million to the caucus and thousands more to individual members.ò[207] The Lorillard tobacco archives had suggested that menthols appealed to ñnegroesò in order to mask a ñgenetic body odorò, and subsequently, William S. Robinson, the executive director of the National African American Tobacco Prevention Network withdrew his support for the FSPTC when menthol was excluded from the list of banned additives.[208] Similar to menthol, there is also much controversy behind the FSPTC Act prohibiting nicotine levels to be decreased to zero. However, the FDA does now have the authority to reduce nicotine yields to very low non-addicting levels, as was suggested in Dr. Kesslerôs proposal. Nicotine reduction in tobacco products could have a profound impact on reducing tobacco-related morbidity and mortality, and in addition to the FSPTC Act, the WHO Framework Convention on Tobacco Control Articles 9-11, also support the establishment of product standards for tobacco constituents including nicotine.[209]In 1994, Benowitz and Henningfield proposed an industry wide incremental and gradual reduction of nicotine

levels of all cigarettes over the period of 10 ï 15 years.[210]The prevalence of smoking would decline from 23% to 5% when using a computer simulation modeling the predictive effects of a reduction in nicotine to non-addictive levels.[211]However, one of the biggest concerns with reduced nicotine cigarettes is that they would lead to ñcompensatoryò smoking behavior to maintain an addictive level of nicotine intake, resulting in the smoker taking in greater levels of toxic smoke and harmful constituents.[212]There may also be unintended consequences such as smokers switching to other drugs or dual use of tobacco products such as smoking a reduced nicotine cigarette and using oral tobacco products at the same time. There may also be a public misconception that the reduced nicotine products are ñsaferò, so non-smokers or quitters may mistakenly use these reduced nicotine products as ñstartersò or ñre-startersò, needlessly exposing them to the other harmful constituents of cigarettes.[213]The FDA will also need to consider the possibility of illicit cigarette marketing, industry manipulation of nicotine analogs, smuggling and internet sales cigarettes with full nicotine content.[214] The tobacco industry documents revealed that the chemical constituents of cigarettes may also increase the amount of free base nicotine once smoked, as was discovered by Dr Kesslerôs team on a site visit observing the addition of ammonia to enhance the bioavailability of nicotine.[215] The ñfreebasingò of nicotine by ammonia allows the nicotine to deliver a more powerful ñkickò, by transforming the nicotine molecule from a bound salt, into a free base, making it more readily available to the body.[216] Even if the FDA would restrict or ban the addition of ammonia to tobacco, manufacturers can control nicotine delivery by various other design and manufacturing techniques such as using high-nicotine tobaccos and also higher nicotine-containing parts (i.e. stems) of the

tobacco leaf to raise the nicotine concentration in low tar cigarettes or adding completely extraneous nicotine.[217] Dr. Kesslerôs investigators had also discovered evidence of the tobacco industry research into attempts at genetically engineering tobacco plants so as to increase their nicotine content as well as exploring pharmacologic analogs that have the same dependency causing effect as nicotine.[218] Cigarette manufacturers also used these clever additive technologies to register low tar readings on smoking machines while administering deceivingly higher levels of nicotine to the smoker since the smoking machines measure only levels of liquid and solid nicotine and are not able to register the concentration in the vapor phase where free nicotine is found.[219] The FSPTC Act now provides for the FDA to have jurisdiction over the manufacturing of tobacco products, although the FDA has not yet provided GMP guidance for the tobacco industry to know what it will take to comply. In reviewing the FDA Center For Tobacco website, there are over 100 warning letters and over 2000 retail inspections, but during an April 5th, 2011 Food and Drug Law Institute Annual Conference, the Director of the FDAôs Center For Tobacco Products, Dr. Lawrence Deyton, admitted that the ñCTP has yet to conduct a manufacturer inspectionò.[220] The concept of GMP and Quality Control of cigarette manufacturing seems counterintuitive when you consider that a cigarette, when designed as intended, and is taken as directed, has been proven to cause addiction, serious illness, cancer and death. There is also the question of escaping liability when a cigarette company can now claim that their product is ñFDA Approvedò. This part of the FSPTC Act is still a work in progress, although a search of the FDA Center For Tobacco website indicated that an April 2012 meeting agenda included a discussion pertaining to the suitability, availability and characterization of tobacco reference standards and laboratory

analyte testing methodology for tobacco product constituents such as pH, nitrosamines, carbon monoxide and polycyclic aromatic hydrocarbons.[221]However, considering that there are over 600 ingredients in cigarettes, and when burned, they create more than 4,000 chemicals, this project will be daunting.[222]Additionally, there will be challenges with the shear enormity of the size of the cigarette manufacturing facilities. When Dr. Kesslerôs team of investigators had only a partial tour of the 750,000 square foot Park 500, which is one of several Phillip Morris facilities, the investigators reported that it would take several months to conduct a formal FDA inspection if they were ever required to do so.[223]In regards to CAPA, the Legacy Tobacco Documents online do have numerous customer complaints archived, ranging from the finding of contaminates such as worms, feces, metal, plastic and other ñforeign matterò, to foul taste, fell apart, and ñflame was so high it burnt my nose and singed my hairò.[224]The obvious challenge that the FDA will now have to consider in regulating the manufacturing of tobacco products, especially in the case of cigarettes, is that tobacco itself is already toxic, as was discussed in Chapter Two of this thesis. Despite envisioning a completely sterile manufacturing facility under the highest conditions of compliance with GMP regulations, the fact remains that even the ñcleanestò cigarette smoke can kill you, so it is rather pointless to worry about contaminants such as worms.[225] Corrective actions would of course resolve the issue of foreign contaminants, but the notion seems rather absurd when you consider that cigarettes and cigarette smoke already contain at least 50 known carcinogens.[226] The FSPTC Act does require the establishment of a list of harmful and potentially harmful constituents (HPHCs) in tobacco products and tobacco smoke, as required by the FD&C Act. There is currently a list of 93 established HPHCôs on the FDA Center For Tobacco

Products website, and they are classified as carcinogens, respiratory toxicants, cardiovascular toxicants, reproductive or developmental toxicants or addictive.[227](Table 3). During the course of Dr. Kesslerôs investigation of the tobacco industry, he writes about a discussion that he had with a confidential informant who claimed that during her job at Philip Morris, she was given a list of the carcinogens in tobacco, and successfully removed most of them via supercritical extraction technology.[228] This is the same methodology used to decaffeinate coffee, yet the company did not pursue any further, and the informant could not offer any explanation why. With the FSPTC Act, we get a list of these harmful ingredients, along with a special rule on pesticides that states that beginning two years after the date of enactment of the FSPTC Act, manufacturers cannot use foreign or domestic tobacco that contains pesticide residues at a level greater than is specified by applicable Federal law for domestically grown tobacco. Shockingly, the FDA Center for Tobacco Products claims that according to the USDA and EPA, there are no established tolerance limits for pesticide chemical residues for domestic tobacco. This is especially alarming considering that scientific studies as well as the cigarette manufacturers have established that the filters in cigarettes are not designed to filter out heavy organophosphate compounds such as those which are found in tobacco pesticides.[229] The filters in cigarettes merely act as ñspeed bumpsò enabling the harmful constituents of smoke to pass on through into the smokersô lungs.[230] The following letter is from the FDAôs Director of the Center For Tobacco Products, Dr. Lawrence Deyton, confirming that there are no EPA or USDA tolerance limits for pesticide chemical residues that apply to domestically grown tobacco, in response to a request from an attorney for R.J. Reynolds.[231]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration **Center for Tobacco Products**

9200 Corporate Boulevard

Rockville, MD 20850-3229

December 6, 2011

James E. Swauger, Ph.D., DABT
Vice President, Regulatory Oversight
R.J. Reynolds Tobacco Company
401 N. Main Street
Winston-Salem, North Carolina 27101

Dear Mr. Swauger:

This is in response to your inquiry on behalf of Philip Morris USA Inc., U.S. Smokeless Tobacco Company LLC, Lorillard Tobacco Company, and Alliance One International, Inc., regarding the special rule on tobacco containing pesticide chemical residue under section 907(a)(1)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Section 907(a)(1)(B) of the FD&C Act establishes that:

> Beginning 2 years after the date of enactment of the Family Smoking Prevention and Tobacco Control Act, a tobacco product manufacturer shall not use tobacco, including foreign grown tobacco, that contains a pesticide chemical residue that is at a level greater than is specified by any tolerance applicable under Federal law to domestically grown tobacco.

This special rule provides that, effective June 22, 2011, manufacturers cannot use any tobacco, whether domestically or foreign grown, that contains a pesticide chemical residue that exceeds any tolerance level established under Federal law that applies to domestically grown tobacco. The Family Smoking Prevention and Tobacco Control Act does not establish any tolerance limits for pesticide chemical residues that apply to domestically grown tobacco. To determine whether there are pesticide residue tolerance levels applicable to domestic tobacco, the Food and Drug Administration (FDA) consulted with the U.S. Department of Agriculture (USDA) and U.S. Environmental Protection Agency (EPA). According to USDA and EPA, under their laws there are currently no established tolerance limits for pesticide chemical residues that apply to domestically grown tobacco. If such a tolerance is established, we plan to provide this information to tobacco product manufacturers.

We note that under the Federal Insecticide, Fungicide, and Rodenticide Act, pesticides generally may not be sold or distributed in the United States unless first registered by EPA. This includes pesticides sold or distributed for use on domestically grown tobacco. As part of the registration process, EPA evaluates the pesticide to, among other things, ensure that it will not pose unreasonable risks to human health or the environment. If you have any additional questions about this provision of the law, please email them to: AskCTP@fda.hhs.gov

Sincerely,

Director, Center for Tobacco Products Lawrence R. Deyton, M.S.P.H., M.D.

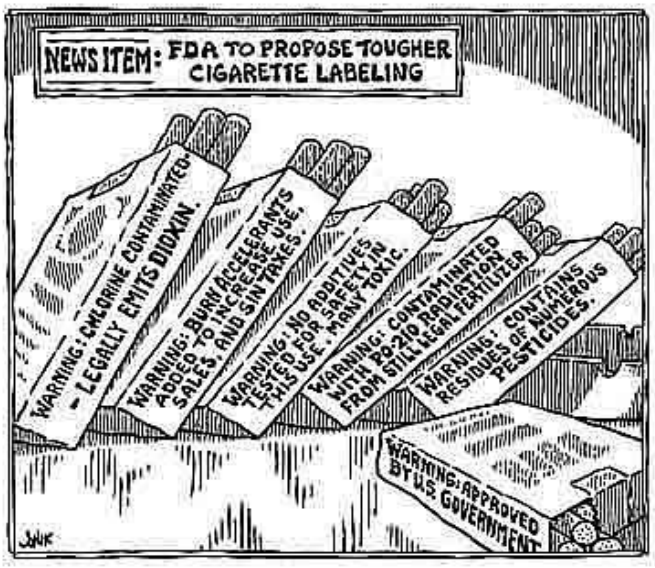
This is alarming considering that the FSPTC Act is using this same pesticide residue standard,(of which there is none), for foreign grown tobacco brought back into the US. Nearly 90 percent of flue-cured and burley tobacco is grown by foreign farmers in at least 78 countries, and with the switch to foreign tobacco, the amount of domestic leaf in each American made cigarette has declined by more than 40 percent.[232] Additionally, this letter was dated 4 months before a lawsuit was filed on behalf of Argentinean tobacco farmers who are suing Altria Group (Philip Morris), Carolina Leaf Tobacco Company, Universal Leaf Tobacco Company, Monsanto, and their affiliates claiming that the US tobacco giants knowingly poisoned the farmers with pesticides and caused ñdevastating birth defectsò in their children.[233] The many birth defects cited in the 55-page complaint include ñcerebral palsy, psychomotor retardation, epilepsy, spina bifida, intellectual disabilities, metabolic disorders, congenital heart defects, Down syndrome, missing fingers and blindnessò.[234] The farmers claimed that Philip Morris Tobacco Company bought their crops and asked them to replace their native crop with a ñnewò type of tobacco that required more pesticides and was going to be used in the manufacturer of cigarettes. This is consistent with Dr. Kesslerôs investigation of tobacco company attempts to grow genetically engineered high nicotine tobacco plants in foreign countries.[235] As discussed in Chapter 2 of this thesis, the tobacco plant is highly sensitive and prone to many diseases, and the genetically engineered tobacco plants are even more fragile. Up to sixteen applications of pesticide are generally recommended during a three-month growing period, and some of the chemicals that are absorbed by the plant and residues will remain in the final finished tobacco product, and others which havenôt been used for years, such as DDT may still be found in the tobacco years later due to the

persistence of these types of chemicals in the soil where tobacco is grown.[236] Maleic Hydrazide is a pesticide growth retardant used to prevent tobacco plant sprouts from growing off the stalks of healthy tobacco plants and although it has been a known carcinogen since the 1960ôs, it is still widely used on tobacco plants around the world and the United States.[237] More than 27 million pounds of pesticides are used in tobacco production in the United States, and tobacco ranks sixth among all agricultural commodities in the amount of pesticides applied per acre, according to the GAO.[238] Tobacco farmworkers can be exposed to these harmful pesticides via several routes, but smoking cigarettes laced with pesticides burns the pyrolized chemicals right into the lungs of a smoker, the long term effects of which are unknown according to the EPA.[239] By performing an online search of the legacy tobacco industry documents, utilizing the search term, òpesticideò, between the years 1970 and 2012, I retrieved 58,313 pesticide related internal tobacco industry documents. These documents revealed examples of cigarette manufacturerôs efforts to keep pesticide residue tolerances dangerously high, as seen in a faxed letter from a pesticide company, to the director of research at Philip Morris, it is suggested that since there would be ñless than a 50% chance of forcing the regulations to allow an MRL (maximum residue level) of 15 ppm., the easiest route would be to ñremove tobacco from the list of commodities requiring an MRLò.[240] This tactic has been discussed before in this thesis as history repeats itself again with the tobacco companies lobbying to remove tobacco from regulations or attempts to change regulations to maintain their existence. My online search efforts also led me to find internal documents related to the obvious conflict of interest between tobacco companies and the pesticide residue testing program at North Carolina State University, where in

one letter, the NCSU Director of the Pesticide Residue Research Laboratory, Dr. T.J. Sheets, is soliciting Philip Morris, Inc. for ñcontributed funds to pay for independent toxicological reviewsé .we now have about $17,000 in the accounté in my judgment, we need to bring the total back to about $50,000.ò[241] In a separate letter, the same NSCU director, Dr. T.J. Sheets, is suggesting that instead of an independent subcommittee to evaluate pesticides, as had been proposed by the recent Tobacco Pesticide Working Group, the tobacco companies should contribute money to pay for ñ1 -3 consultantsò, and offered that, òan arrangement could be made with an accounting firm to receive and disburse the monies.ò[242] In performing additional searches pertaining to individual pesticides, for example, òdicambaò, returned 7,781 documents. I learned that dicamba was used to accelerate the ripening of tobacco plants, although this was not a registered use for this pesticide. However, in a letter from Lorillard Tobacco Company to the Dean of North Carolina State University, there is a request to have their Director of Pesticide Research, (the same Dr. T.J. Sheets mentioned above),propose to an upcoming Agricultural Chemicals Advisory Committee meeting that he recommend to the full committee on Pesticide Certification and Testing that it ñseek to have the tolerance for Dicamba residues on tobacco raised from 0.5 ppm to 5.0 ppm.ò[243] Researchers at the University of California in San Francisco performed a case study of approximately 2000 of the internal tobacco industry documents, along with 3,885 government EPA documents, and concluded that the tobacco industry is ñable to exert considerable influence over the pesticide residue regulatory processò.[244] Ultimately, by establishing very low limits on harmful tobacco pesticide residues for both domestic and foreign tobacco, the FSPTC Act could have a major positive impact on public health, especially

considering the substantial quantity of tobacco that is not grown domestically, but is used to manufacture cigarettes in the United States. Unfortunately, even though the FSPTC Act has now given the FDA jurisdiction concerning pesticide residues in tobacco, the politics involved between the tobacco industry and the pesticide regulatory agencies may inhibit any further action since the EPA and USDA maximum pesticide residue limits are still undefined.

Figure 7:



Cartoon by John Jonik - http://wafreepress.org/article/090712substances.shtml

4.2 THE SWEET DEAL

As discussed in Chapter 2 of this thesis, both the Federal Cigarette Labeling and Advertising Act (FCLAA) of 1965, and the Comprehensive Smokeless Tobacco Health Education Act (CSTHEA) of 1986, regulated the manufacture, packaging, and distribution of tobacco and tobacco products, and also granted the Department of Health and Human Services (HHS) the authority to review lists of ingredients added to the tobacco, and to report to Congress on any perceived health effects of any added ingredients.[245] The FSPTC Act of 2009 includes an ongoing review of additive ingredients, as well as a ban on flavorings, (with the exception of menthol). Cigarettes and their components, such as filters and papers, that contain certain characterizing flavors, are now considered adulterated under the Federal Food, Drug, and Cosmetic Act, as amended by the Family Smoking Prevention and Tobacco Control Act. This means that it is now illegal to manufacture, distribute, sell or import into the United States cigarettes that contain characterizing flavors such as herb, spice, or fruit flavors, including cinnamon, vanilla, chocolate, clove, strawberry, grape or cherry. This is a special rule for cigarettes, under Section 907 of the FSPTC Act:

ó“SEC. 907. TOBACCO PRODUCT STANDARDS.
ó(a) IN GENERAL.ð
ó(1) SPECIAL RULES.ð
ó(A) SPECIAL RULE FOR CIGARETTES.ð Beginning 3 months after the date of enactment of the Family Smoking Prevention and Tobacco Control Act, a cigarette or any of its component parts (including the tobacco, filter, or paper) shall not contain, as a constituent (including a smoke constituent) or additive, an artificial or natural flavor (other than tobacco or menthol) or an herb or spice, including strawberry, grape, orange, clove, cinnamon, pineapple, vanilla, coconut, licorice, cocoa, chocolate, cherry, or coffee, that is a characterizing flavor of the tobacco product or tobacco smoke. Nothing in this subparagraph shall be construed to limit the Secretaryôs authority to take action under this section or other sections of this Act applicable to menthol or any artificial or natural flavor, herb, or spice not specified in this subparagraph.ò[246]

This Special Rule of the FSPTC Act does have its merits in that it is intended to reduce the appeal of sweet or candy flavored cigarettes targeted towards kids. However, as

discussed earlier in this thesis, the exclusion of menthol is highly controversial. The tobacco industry fought very hard to exclude menthol from the FSPTC Act, as it is the characterizing flavor of more than 25% of all cigarettes sold, whereas the banned sweet flavors listed above only affect less than 1% of the cigarette market.[247]Of even greater impact would have been a ban on the addition of sugar, as was discussed earlier in this thesis (Chapter 2, p.19). Recall that the addition of sugar to tobacco resulted in the success of the American blended cigarette, and in combination with flu-curing, makes cigarettes more inhalable by dilating the airways, allowing the smoke to travel deeper into the lungs.[248]Similar to the old adage, but with a sinister twist in this case, a spoon full of medicine makes the ñpoisonò go down. From a chemical standpoint, once sugar is burned, it produces acetaldehyde, which interacts with nicotine to intensify psychopharmacologic addiction .[249]I should also point out that acetaldehyde is the first constituent listed on the FDA Center For Tobacco Established List of the Chemicals and Chemical Compounds Identified by the FDA as Harmful, where it is classified as a carcinogen, respiratory toxicant and addictive.(Appendix C). Additional toxic and carcinogenic compounds are generated from the pyrolysis of sugar when smoking, including formaldehyde, acetone, furfural and acrolein.[250]These chemicals all appear on the FDA HPHC list (Appendix C), and recall that as mentioned in Chapter 2 of this thesis, Thomas Edison warned about the health dangers of acrolein in his 1914 letter to Henry Ford.[251] Caramel and other invert sugars were also excluded from the FSPTC Act list of banned sweeteners, even though they produce catechol when burned, another carcinogen on the FDA HPHC list.[252]The exclusion of these sugars led me to investigate the biological effects of inhaling these pyrolysis end products, given my interest and

work experience in the field of diabetes. Smoking is already a well-known risk factor for coronary heart disease, and is has already been proven that smoking aggravates the micro and macro vascular complications of type 2 diabetes.[253]Smoking is also an independent risk factor for the development of insulin resistance and type 2 diabetes, although the mechanisms for smoking-induced insulin resistance are unclear.[254]A PubMed literature search on this topic led me to 1737 publications on the subject of tobacco and diabetes, and although it is beyond the scope of this thesis, I want to point out the relevancy of some key highlights from my findings. In a 2007 study published in JAMA by Willi et al, the risk of insulin resistance and development of type 2 diabetes was independent of and higher than smoking related vascular effects.[255]A 2005 study published in Metabolism by Yoshikawa et al reveals that nicotine receptors are found on the pancreatic islet cells, and that nicotine increases the apoptosis of islet beta cells.[256] A study by Hectors et al, published in the 2011 issue of Diabetologia, reviewed the effect of pesticides on disruption of beta cell function in the pancreas and diabetes progression, which is particularly relevant to this thesis since many of the organophosphate pesticides listed are used on tobacco as mentioned in the previous section.[257] Most recently, a 2012 study published in Diabetes by Bergman et al, showed a reversible mechanism of smoking induced insulin resistance within 1-2 weeks of smoking cessation.[258]A search of the Legacy Tobacco Documents online database by the term, ñdiabetesò, resulted in 46,189 documents, several were related to grants paid to diabetes researchers, along with various clinical trials and journal articles. One study and accompanying newspaper article showed up on file in each of the major tobacco company archives, pertaining to a study by Passey et al, which was published in the 1972 issue of the International Journal

of Cancer, and was titled,òThe Sugar Content and the pH of the Smoke of Cigarette, Cigar and Pipe Tobaccos in Relation to Lung Cancer.ó[259] Dr. Passeyôs research had concluded that in those countries where the sugar content of cigarettes is the lowest, there is a corresponding lower lung cancer death rate, and conversely, those countries that have the highest content of sugar in cigarettes, have the highest lung cancer deaths.[260]Subsequent searches of the online tobacco documents for ñPasseyò, led me to 6386 documents, including internal meeting agendas related to this particular publication, meeting minutes and a dossier pertaining to Dr. Passer.[261] There were also subsequent journal articles published by tobacco company scientists refuting the negative effects of adding sugar to tobacco, which would be expected, given the importance of sugar to facilitate deep inhalation and addiction.[262] By amending the FD&C Act, the FDA now has the jurisdiction to ban sugar as an additive, as outlined in section 907(a)(1)(A) of the FSPTC Act. Under section 902 of the FD&C Act, failure to comply would mean the product is adulterated and subject to seizure. However, the FDA would have to be very descriptive in capturing the additional sugar ñproductsò in their ban, such as honey, molasses, high fructose corn syrup, beet juice, etc., otherwise the tobacco companies could easily utilize a sugar substitute. The elimination of sugar, and sugar products would have a substantial impact on preventing the deep inhalation of cigarettes along with their toxic constituents and the subsequent facilitation of nicotine delivery. The WHO FCTC, (World Health Organization Framework Convention on Tobacco Control), just announced that on March 13, 2012, Brazil has just banned all flavors, including menthol and additives such as sweeteners and ammonia, from all tobacco products.[263] This is the strongest ban on flavors and additives in the world, and will hopefully be the

global precedent that will inspire the FDA to take similar action. Dr. Kessler had echoed the same sentiment during our teleconference interview. However, the United States has yet to ratify the WHO FCTC, (World Health Organization Framework Convention on Tobacco Control). Although President Bush signed the treaty with great fanfare in May 2004, it was never sent to the senate for ratification.[264]While President Obama supported the ratification of the WHO FCTC when he was still serving in Congress, the current political capital is devoted to the FSPTC Act of 2009, making it unlikely that the required two-thirds majority of the Senate would agree to ratify .[265] Ironically, the provisions of the WHO FCTC closely resemble the provisions of the FSPTC Act, including price and tax measures to reduce the demand for tobacco, measures to reduce promotion to youth, regulation of contents, packaging, labeling, advertising, and protection against exposure to tobacco smoke.[266]The FSPTC Act includes a controversial provision which requires tobacco industry participation in the Tobacco Products Scientific Advisory Committee, which makes it even more unlikely that the United States will ever ratify the treaty, since the WHO FCTC article 5.3 prohibits this type of interaction.[267] The WHO FCTC article 5.3 specifically acknowledges that the ñtobacco industry has operated for years with the express intention of subverting the role of governments and of WHO in implementing public health policies to combat the tobacco epidemicò, and recognizes the ñneed to be alert to any efforts by the tobacco industry to undermine or subvert tobacco control efforts as well as the need to be informed of activities of the tobacco industry that have a negative impact on tobacco control effortsò.[268] An online search of the legacy tobacco documents led to an Inter Office Memo from executives at Philip Morris who found it ñvery encouragingò that the Danish government announced its reduction in payment to

the WHO by half, from $10.89 million to $5.6 million.[269]Two additional tobacco industry briefing papers revealed that both the British American Tobacco Company and Philip Morris cultivated relationships with tobacco friendly governments, including the United States, to attempt to weaken the FCTC.[270]To date, the United States is one of the only few countries which has signed, but not yet ratified the WHO FCTC(Appendix F).

The FSPTC ACT provision for the inclusion of tobacco industry representatives on the advisory panel of the FDA Tobacco Products Scientific Advisory Committee has created a conflict of interest in that the major tobacco companies were convicted of racketeering charges under the RICO Act in 2006 after misleading the public for years about the health hazards of smoking.[271] Conversely, the tobacco industry has sued the FDA, contending that the scientific members of the advisory committee have conflicts of interest that have ñtainted any recommendations by the panel to the agency.ò[272]The tobacco companies have alleged that some of the scientific members of the TPSAC have served as paid expert witnesses in previous lawsuits against the tobacco industry, and also received money from drug companies that make nicotine-replacement products or other smoking-cessation products. Both the Lorillard Tobacco Company and Altria Company websites contain links to letters of protest written to Dr. Lawrence Deyton, the Director of the FDA Center for Tobacco Products, expressing their objections to the TPSAC disseminating of scientific literature and data pertaining to the use of menthol in cigarettes, and the development of the list of harmful constituents in tobacco.[273] In addressing these issues with the TPSAC, Dr. Margaret Hamburg, the current FDA Commissioner, explained, ñI want to underscore it once again, that the FDA regulation of tobacco products is a science based, science driven process. It must be.ò[274]

4.3 CIGARETTES ï DRUGS, DEVICES OR DREGS?[275]

The FSPTC Act recognizes the earlier efforts of Dr. Kessler in acknowledging that nicotine is an addictive drug, and that the major US cigarette companies have knowingly designed their cigarettes to precisely control nicotine delivery levels and provide doses of nicotine sufficient to create and sustain addiction, while also concealing much of their nicotine related research.[276]

Menthol is also a drug, either derived from natural sources or synthesized, that is widely used in consumer and medicinal products. [277] Menthol has long been used in cigarettes as a flavor-characterizing additive, to ñcoolò down the cigarette smoke making it less harsh and easier to smoke/inhale.[278] Menthol is also an active pharmaceutical ingredient in many medical products, as either the sole pharmaceutical ingredient, as in throat lozenges or one among many such ingredients as in a cold or cough medicine. Menthol is regulated as a drug with restrictions on allowable doses and uses, and requirements with respect to instructions for use and warnings. However, when used in cigarettes, menthol is not regulated according to the safety standards applied to food and drugs, and it remains currently exempt from FDA jurisdiction under the FSPTC Act.

Much of the historical regulatory struggles pertaining to the FDA regulation of tobacco have stemmed from the debate whether to classify cigarettes as drugs, devices, or combination drug delivery device as was seen in Dr. Kesslerôs Proposed Rule. As discussed throughout this thesis, this became the regulatory sticking point in virtually every attempt towards granting FDA jurisdiction. The statutory definitions according to the FD&C Act of 1938 and the Pure Food and Drug Act of 1906 both had no clear distinctions for cigarettes, or consideration of FDA regulation thereof.[279]

The FSPTC Act of 2009 has provided that tobacco products are neither a drug, device, or combination with an amendment added to the FD&C Act (21 U.S.C. 321).[280]

The FSPTC Act of 2009 is built around a public health standard that represents a drastic departure from the traditional ñsafety and efficacyò standard in the Food, Drug and Cosmetic Act, which has historically been the source of regulatory angst in previous attempts towards FDA jurisdiction. This was particularly evident when examining the core mission of the FDA which includes ñprotecting the public health by ensuring that drugs are safe and effective, and that there is reasonable assurance of the safety and effectiveness of devices intended for human use.ò[281] Additionally, the FD&C Act requires premarket approval of any new drug, giving the FDA the right to ñrefuse to approve the application of a new drug if it is not safe and effective for its intended purpose.ò[282] The FD&C Act also requires the FDA to classify all devices into one of three categories, where there must be a ñreasonable assurance of the safety and effectiveness of the device.ò [283] The ñrestricted deviceò category provision would allow the FDA to place conditions on the sale or distribution of a device specifically when ñthere cannot otherwise be reasonable assurance of its safety and effectivenessò, and the FD&C Act would essentially require the FDA to prevent the marketing of any drug or device where the ñpotential for inflicting death or physical injury is not offset by the possibility of therapeutic benefit.ò[284] Under literal interpretations of the FD&C Act, cigarettes would have to be removed from the market, an although the FDA and Dr. Kessler made very strong cases in support of jurisdiction, Congress, no doubt under the heavy influence of tobacco industry lobbyists, precluded the FDA from regulating tobacco products.[285] What we have now, with the 2009 FSPTC Act, is an obligation that

the FDA is to regulate tobacco products in a manner that is ñappropriate for the protection of public healthò.[286] Along with creating a new ñPublic Health Standardò for tobacco product regulation, the FDAôs traditional standard of ñsafe and effectiveò now does not apply to tobacco products because there is no such thing as a ñsafeò tobacco product. Just as there is no such thing as a ñsafeò guillotine, or a ñsafeò bullet, or ñsafeò way to drown, we are going to see the same endpoint here, and that unfortunately, is death no matter how ñcleanò and ñsafeò we try to make cigarettes.

However, by requiring changes in tobacco products, the FDA could now require the removal of harmful ingredients or the reduction of nicotine levels, to make tobacco products less harmful and less addictive. Because nicotine and menthol both fall within the FD&C definition of drug, this would best be accomplished by prohibiting tobacco products to deliver a pharmacologic dose of these two drugs. Alternatively, the FDA could require that these drugs not be delivered via combustion, which would help shift current tobacco users who were unwilling to quit smoking to less harmful products such as nicotine patches to treat their addiction. This would also be a viable solution to the detrimental effects of smoking carcinogenic pyrolysis endproducts as was discussed in Section 4.2 of this thesis. The WHO FCTC also supports alternatives to cigarettes and promotes switching from smoking to non-combustible forms of nicotine delivery as part of their overall strategy to reduce tobacco harm and the burden of disease.[287]

CONCLUSIONS:

This thesis examined the evolution of significant attempts by the FDA to regulate tobacco from the late nineteenth century to present day, along with the political influences impacting these regulatory decisions. I provided the background into the early history and chemistry of the tobacco plant constituents, along with the invention of flue-curing which along with the addition of sugar, ultimately led to the dangerous inhalation of tobacco. A glimpse into the early perspective of Dr. Harvey Wiley was presented, as well as a prophetic revelation from Thomas Edison, and references to Dr. David Kesslerôs contribution towards current tobacco regulations, up to and including the Tobacco Control Act signed by President Obama. This paper compared and contrasted the legal and cultural definitions of ñdrugò, and explored the historical challenges that the FDA has faced when trying to invoke this literal definition into its efforts to regulate tobacco. Finally, this thesis examined the political influence of the tobacco industry and economic considerations which have greatly influenced the limitations of the FDAôs authority in fully regulating tobacco. I would conclude that from all perspectives, the FDA is the most logical place for tobacco jurisdiction to be placed, but there must be coordination and cooperation with other governmental agencies such as the USDA, EPA, NIH, FTC, ATF and global organizations such as the WHO FCTC. I provided examples of tobacco industry attempts to impact regulations within each of these agencies, and it is clear that the tobacco companies still have a ñseat at the tableò in current FDA regulatory decision making. To be successful, the FDA will need to create the standards which will ensure that all tobacco products currently on the market, as well as new ones are

appropriate for the protection of public health. Both Dr. Kessler and Dr. Hamburg have stressed the importance of science in making the appropriate regulatory decisions moving forward. However, history has demonstrated that no clear answers flow from this scientific analysis. Instead, the answers have often flowed from policy or societal judgment and political considerations. If there is to be any progress in this effort, the FDA must not base its decisions on non-scientific compromises resulting from tobacco industry influences. The FSPTC Act now grants the FDA the authority it needs to halt the single most preventable cause of disease, disability and death in the United States today, and it must not hesitate to take the necessary steps to do so.

APPENDIX A:

American Lung Association's Battle Against Tobacco Use Milestones – Tobacco Timeline

2011: Nevada becomes the first state to weaken its smokefree law. 2011 also marks the first year since 2001 that no state passed a comprehensive smokefree law.

2011: The Food and Drug Administration reveals the new graphic warning labels that are set to appear on cigarette packs starting in 2012

2010: Kansas passes a comprehensive smokefree law, bringing the total of smokefree states to 27 + the District of Columbia, and putting the country over halfway towards accomplishing the Lung Associationôs Smokefree Air Challenge.

2010: President Obama signs the Patient Protection and Affordable Care Act into law. The law includes important provisions that will expand tobacco cessation benefits and establishes the Prevention and Public Health Fund, which provides funds to prevent and reduce tobacco use.

2010: Youth access and marketing restrictions on tobacco products take effect and cigarette companies are prohibited from using ñlightò, ñlowò and other misleading health descriptors.

2010: U.S. Surgeon General releases 30th Surgeon Generalôs report on tobacco entitled, *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease*.

2009: President Obama signs legislation granting the U.S. Food and Drug Administration regulatory authority over tobacco products. Tobacco products are now no longer exempt from basic oversight.

2008: The American Lung Association launches its State Tobacco Cessation Coverage Database, which tracks what each state covers to help smokers quit. This database, available at www.lung.org/cessationcoverage is the only comprehensive, up-to-date source for information on coverage of cessation treatments for Medicaid recipients, state employees, and laws requiring private health insurance plans to cover quit smoking treatments.

2008: The U.S. Public Health Service releases an important update to its Guideline on Treating Tobacco Use and Dependence. This guideline contains recommendations for doctors on how to help their patients quit using tobacco, and recommends the use of 7 medications and 3 types of counseling to help people quit.

2007: The U.S. Centers for Disease Control and Prevention updates the *Best Practices for Comprehensive Tobacco Control Programs* refining the evidence-based recommendations effective tobacco control programs to prevent and reduce tobacco use.

2006: Judge Kessler releases her final ruling in the U.S. Department of Justiceôs federal suit against the tobacco companies. She finds that the tobacco industry had lied for 50 years and deceived the American public on health issues and marketing to children.

2006: The American Lung Association launched its Smokefree Air Challenge, urging all states and the District of Columbia to pass comprehensive smokefree laws that protect people and workers from secondhand smoke.

2006: The Surgeon General releases *The Health Consequences of Involuntary*

Exposure to Tobacco Smoke. The report said unequivocally that the "debate is over" ï secondhand smoke in any form at any level is harmful to health.

2005: After over a year of court proceedings in the U.S. Department of Justiceôs suit against the tobacco companies, the Department announced that it was reducing the amount of remedies it was seeking in the case by billions of dollars. Six major public health groups, including the American Lung Association, intervene in the lawsuit to advocate for stricter remedies to preclude future tobacco industry wrongdoings.

2004: The United States signs the Framework Convention on Tobacco Control Treaty, which is the worldôs first tobacco control treaty and establishes international guidelines for countries to implement and control tobacco use and addiction. The treaty has not yet been sent to the U.S. Senate for ratification.

2002: The American Lung Association releases the first edition of the *State of Tobacco Control* report. This report, available at www.stateoftobaccocontrol.org, tracks progress on key tobacco control policies at the state and later the federal level and assigns grades to state laws and regulations. It is released annually in January.

2002: The result of advocacy work led by the American Lung Association, Delawareôs statewide smokefree law goes into effect. Delaware was the first state in four years to pass a smokefree law, and this event was the catalyst for many other states to go smokefree in the 2000ôs.

2000: The U.S. Supreme Court rules in a 5-4 decision that the U.S. Food and Drug Administration could not assert authority over tobacco products without being given the power to do so by Congress. Efforts turn to Congress to pass legislation.

1999: The U.S. Centers for Disease Control and Prevention releases the first edition of *Best Practices for Comprehensive Tobacco Control Programs*. This document details how state tobacco control programs should be structured to best prevent smoking and help smokers quit. It also recommends minimum funding levels at which each state can best run these programs.

1999: The U.S. Department of Justice announces it is suing the tobacco industry under the RICO statute ï the same statute used to prosecute the Mob ï claiming the tobacco industry engaged in a ñcoordinated campaign of fraud and deceit.ò

1998: Attorneys General from 46 states and the tobacco industry reach the landmark Master Settlement Agreement to reimburse state government for tobacco-related health care costs. The billions of dollars were supposed to be used to prevent smoking and help people quit, unfortunately states have used the majority of this money for other, unrelated purposes.

1998: California becomes the first state in the nation to eliminate smoking in bars. This law, along with the law eliminating smoking in restaurants and most other public places, makes California the first state to pass a comprehensive statewide smokefree air law. The American Lung Association was one of the organizations leading the campaign for this law.

1996: American Lung Association assumes responsibility for publishing State Legislated Actions on Tobacco Issues. This record is still maintained and updated, and is available at http://slati.lungusa.org.

1995: In response to a letter from the American Lung Association and its public health partners, the U.S. Food and Drug Administration asserts jurisdiction over tobacco products by declaring nicotine a drug. President Clinton approves this proposal in 1996, giving the agency authority to regulate cigarettes as a ñdrug delivery device.ò

1994: Seven tobacco company executives testify before Rep. Henry Waxmanôs congressional committee that they do not believe nicotine is addictive.

1993: The U.S. Environmental Protection Agency published *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders*. The report concludes that secondhand smoke is responsible for approximately 3,000 lung cancer deaths each year in nonsmoking adults and impairs the respiratory health of hundreds of thousands of children.

1990: San Luis Obispo, California becomes the first city in the world to eliminate smoking in all public buildings, including bars and restaurants.

1989: A bill spearheaded by Sen. Frank Lautenberg (D-NJ) and Rep. Dick Durbin (D-IL) passed Congress banning smoking on all domestic airlines. The American Lung Association was one of the public health groups leading efforts to pass this law.

1988: Tobacco Free America (American Lung Association, American Heart Association and American Cancer Society) publish *State Legislated Actions on Tobacco Issues*. This document tracked tobacco control policies ï like tobacco taxes, smokefree air laws, and tobacco control program funding ï for every state.

1988: California voters approve Proposition 99, which increased the cigarette tax by 25 cents and dedicated some of the revenue to create the first comprehensive statewide tobacco control program in California. It was also the first time a state dedicated proceeds from tobacco taxes to help prevent and stop smoking. The American Lung Association was instrumental in the passage of this proposition, and subsequent support for the California Tobacco Control Program.

1987: The RJ Reynolds tobacco company debuts the Joe Camel character in its

U.S. advertisements. This cartoon character hooked millions of kids on Camel tobacco products.

1987: Aspen, Colorado becomes the first city in the United States to require smokefree restaurants.

1987: Congress prohibits smoking on domestic flights of less than two hours. Takes effect in 1988.

1986: The 19th Surgeon Generalôs report on *The Health Consequences of Involuntary Smoking* is published. This report first officially acknowledged and emphasized the harmful effects of secondhand smoke.

1984: The U.S. Food and Drug Administration approves nicotine gum as the first drug designed to help people quit smoking.

1975: The Minnesota Clean Indoor Air Act goes into effect. This is the first statewide law in the nation that requires separate smoking areas in public places.

1968: Philip Morris introduces the Virginia Slims brand. With its iconic ñYouôve come a long way babyò ad campaign targeting women.

1966: Health warnings first appear on cigarette packs in response to congressional legislation. The warnings read, ñCautionð cigarette smoking may be hazardous to your health.ò

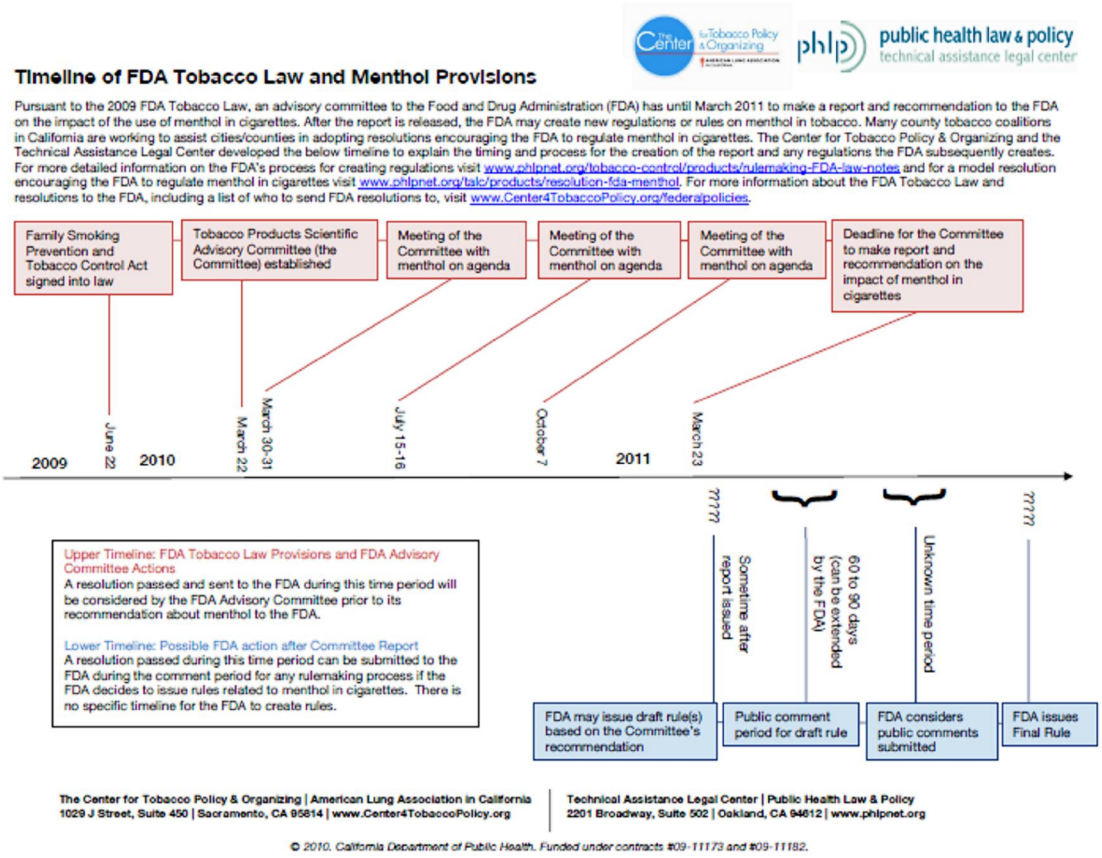
1964: Surgeon Generalôs report on smoking is published: *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service,* states proven link between smoking and lung cancer.

1961: The American Lung Association, along with its public health partners, write to President Kennedy, highlighting the increasing evidence of the health hazards of smoking and urging him to establish a commission to address the problem. This letter led to the publishing of the landmark Surgeon Generalôs report in 1964.

1954: Richard Doll and A. Bradford Hill, publish an article in the British Medical Journal that confirms the link between smoking and lung cancer.

Reference:

(http://www.stateoftobaccocontrol.org/our-fight/tobacco-timeline.html)



Appendix B: Timeline of FDA Tobacco Law and Menthol Provisions

Reference:

(http://www.center4tobaccopolicy.org/CTPO/_files/_file/Timeline%20of%20FDA%20Tobacco%20Law%20and%20Menthol%20Provisions%20November%202010.pdf)

Appendix C

TABLE 1—ESTABLISHED LIST OF THE CHEMICALS AND CHEMICAL COMPOUNDS IDENTIFIED BY FDA AS HARMFUL AND POTENTIALLY HARMFUL CONSTITUENTS IN TOBACCO PRODUCTS AND TOBACCO SMOKE

Constituent	Carcinogen (CA), Respiratory toxicant(RT), Cardiovascular toxicant(CT)reproductive or developmental toxicant(RDT) addictive (AD)
Acetaldehyde	CA, RT, AD
Acetamide	CA
Acetone	RT
Acrolein	RT, CT
Acrylamide	CA
Acrylonitrile	CA, RT
Aflatoxin B1	CA
4-Aminobiphenyl	CA
1-Aminonaphthalene	CA
2-Aminonaphthalene	CA
Ammonia	RT
Anabasine	AD
o-Anisidine	CA
Arsenic	CA, CT, RDT
A-a-C (2-Amino-9*H*-pyrido[2,3-*b*]indole)	CA
Benz[*a*]anthracene	CA, CT
Benz[*j*]aceanthrylene	CA
Benzene	CA, CT, RDT
Benzo[*b*]fluoranthene	CA, CT
Benzo[*k*]fluoranthene	CA, CT
Benzo[*b*]furan	CA
Benzo[*a*]pyrene	CA
Benzo[*c*]phenanthrene	CA
Beryllium	CA
1,3-Butadiene	CA, RT, RDT
Cadmium	CA,CD,RDT
Caffeic acid	CA
Carbon monoxide	RDT
Catechol	CA
Chlorinated dioxins/furans	CA, RDT
Chromium	CA, RT, RDT
Chrysene	CA, CT
Cobalt	CA, CT
Coumarin	
Banned in food	
Cresols (o-, m-, and p-cresol)	CA, RT
Crotonaldehyde	CA
Cyclopenta[*c,d*]pyrene	CA
Dibenz[*a,h*]anthracene	CA
Dibenzo[*a,e*]pyrene	CA
Dibenzo[*a,h*]pyrene	CA
Dibenzo[*a,i*]pyrene	CA
Dibenzo[*a,l*]pyrene	CA
2,6-Dimethylaniline	CA
Ethyl carbamate (urethane)	CA, RDT
Ethylbenzene	CA
Ethylene oxide	CA, RT, RDT
Formaldehyde	CA, RT
Furan	CA
Glu-P-1 (2-Amino-6-methyldipyrido[1,2-*a*:3ô2ô*d*]imidazole)	CA

Appendix C con't).

ESTABLISHED LIST OF THE CHEMICALS AND CHEMICAL COMPOUNDS IDENTIFIED BY FDA AS HARMFUL AND
POTENTIALLY HARMFUL CONSTITUENTS IN TOBACCO PRODUCTS AND TOBACCO SMOKEð Continued

Glu-P-2 (2-Aminodipyrido[1,2-*a*:3ô2ê*d*]imidazole) ..... CA
Hydrazine ..... CA, RT
Hydrogen cyanide ..... RT, CT
Indeno[*1,2,3-cd*]pyrene ..... CA
IQ (2-Amino-3-methylimidazo[4,5-*f*]quinoline) ..... CA
Isoprene ..... CA
Lead ..... CA, CT, RDT
MeA-a-C (2-Amino-3-methyl)-9*H*-pyrido[2,3-*b*]indole) ..... CA
Mercury ..... CA, RDT
Methyl ethyl ketone ..... RT
5-Methylchrysene ..... CA
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) ..... CA
Naphthalene ..... CA, RT
Nickel ..... CA, RT
Nicotine ..... RDT, AD
Nitrobenzene ..... CA, RT, RDT
Nitromethane ..... CA
2-Nitropropane ..... CA
N-Nitrosodiethanolamine (NDELA) ..... CA
N-Nitrosodiethylamine ..... CA
N-Nitrosodimethylamine (NDMA) ..... CA
N-Nitrosomethylethylamine ..... CA
N-Nitrosomorpholine (NMOR) ..... CA
N-Nitrosonornicotine (NNN) ..... CA
N-Nitrosopiperidine (NPIP) ..... CA
N-Nitrosopyrrolidine (NPYR) ..... CA
N-Nitrososarcosine (NSAR) ..... CA
Nornicotine ..... AD
Phenol ..... . RT, CT
PhIP (2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine) ..... CA
Polonium-210 ..... CA
Propionaldehyde ..... RT, CT
Propylene oxide ..... CA, RT
Quinoline ..... CA
Selenium ..... RT
Styrene ..... CA
o-Toluidine ..... CA
Toluene ..... RT, RDT
Trp-P-1 (3-Amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole) ..... CA
Trp-P-2 (1-Methyl-3-amino-5*H*-pyrido[4,3-*b*]indole) ..... CA
Uranium-235 ..... CA, RT
Uranium-238 ..... CA, RT
Vinyl acetate ..... CA, RT
Vinyl chloride ..... CA

Dated: March 23, 2012.
Leslie Kux,
Assistant Commissioner for Policy.
[FR Doc. 2012-7727 Filed 3-30-12; 11:15 am]
BILLING CODE 4160-01-P

http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM297981.pdf (Accessed 11/09/2012).

Appendix D ï Smoking Quotes

"One of the strong arguments against smoking is that it turns gentlemen into rowdies, in some cases, in the fundamental matter of consideration for others. Another is the representative statement made by the National Board of Underwriters that "careless smokers were responsible for the greatest amount of fire loss from 1916 to 1921." The report was for the District of Columbia, but there is no reason for thinking the National Capital is worse than other places in this respect.

What does tobacco do to us? There is in it a poison called nicotine so deadly that one full drop of it would kill an adult. A smaller portion of it taken for the first time by a boy makes him deathly sick. That gives warning of its poisonous character, but doesn't usually wean him from the folly. It did not in my case, for I speak as an ex-smoker. I quit at the end of my first week, after. I had got over the nausea and had begun to enjoy "a good cigar." But I had already discovered that tobacco would hobble my brain and lead others to follow my bad example. Tobacco of any kind puts a soft-pedal on efficiency of mind and body. It puts us in a state of narcosis. We are half chloroformed. The Literary Digest of April 15, 1922, records a test of the effects of tobacco on efficiency at Stanford University. Telegraph operators of three kinds were selected for the test. None of them smoked on duty. Those who smoked much when off duty were regarded as "heavy smokers." Their percentage of efficiency was 38. Those who smoked two pipes a day or one cigar, or two or three cigarettes before and after work and at noon, were regarded as "light smokers." Their efficiency was 40.1. The women operators, non-smokers, though of the "weaker sex," excelled both the other groups with an efficiency record of 46.6. The nicotine not only dulls our nerve cells, but kills some of them. If you have brains to burn, a tobacco bonfire is a good way to get rid of the surplus. One criminal lawyer argued jocosely to me that it was better for the world that he should smoke as he could in that case do less harm in his profession. I seriously agreed that was one of the many cases where "truth had been spoken in jest." If your work for the world is a curse, the more you dull your powers and shorten your life through "Lady Nicotine," the better. Speaking of "Lady Nicotine," a name that gets new significance because women are beginning to smoke, I am reminded to quote what U. S. Surgeon General Hugh S. Cummings has said about women smoking: "The cigarette habit indulged in by women tends to cause nervousness and insomnia. If American women generally contract the habit, as reports now indicate they are doing, the entire American nation will suffer. The physical tone of the whole nation will be lowered. This is one of the most evil influences in American life today. The number of American women who are smoking cigarettes is amazing. THE HABIT HARMS A WOMAN MORE THAN IT DOES A MAN. The woman's nervous system is more highly organized than the man's. The reaction, therefore, is more intense, ruining her complexion, causing it to become gradually yellow and ashen.

Hudson Maxim, one of the world's greatest writers on munitions and inventor of the bomb-proof ship, said during the World War : "The numbers of our men killed and the number injured by all the poisonous gases of and injured by the poisonous gases or cigarette smoke Germans will be far fewer than those who will be killed which our hyper-sentimentality is inflicting upon them, while the after effects will be even worse. I do not for one minute mean to imply that cigarette smoke is as virulent a poison as the gases employed against our troops by the Germans, but I do mean that cigarette smoke will be *responsible for a larger number of deaths than the poisonous gases of the Germans, and I claim that the permanent effects of the cigarette poison are even worse than the after effects of the poisonous gases of the Germans, be-cause while the German gases. affect the body they do not, like the cigarette, impair the mind"- (*Dr. Harvey W. Wiley, in a 1922 annual session of the Chamber of Commerce in Washington D.C.)

Reference: http://freedomofmedicineanddiet.blogspot.com/2011/04/

Appendix E:

Teleconference Transcript - November 12, 2012 at 5:00 p.m.(EST).

Title: Joy Sherrick interview with Dr. David Kessler, Former Commissioner of the FDA.

University of Georgia Research Project Number: 2013-10255-0
Principal Investigator: Dr. Paul Brooks

Joy: Hello Dr. Kessler, this is Joy Sherrick. Is this a good time for you to speak? Paulette has faxed me your signed consent form, do you have any questions before we start?

Dr. Kessler: This is fine...good...yes, Paulette has taken care of the consent form. I am literally on the run, getting in out of cars and not in front of computer right now, go ahead and start if we need more time, we'll find it..... I apologize, I am jumping in and out of cars.

Joy: What does FDA control of tobacco really mean, and how far have we come since you were the Commissioner of the FDA?

Dr. Kessler: You have to remember, when we started out, tobacco was not regulated,....only by the bureau of alcohol, tobacco and fire arms, and then, only for tax purposes.
What's really important, is how society has looked at the product,the most important change, not just Federal regulation over the last 10 years.... so then consider instead how societal norms have changed.

Joy: Do you think that we will ever see a reduction of nicotine down to sub therapeutic levels in our lifetime?

Dr. Kessler: It needs to happen....I talk about it...it absolutely needs to happen. FDA has the authority, but it needs to understand the scientific basis of what it needs to do. What is sub therapeutic, I don't think we know. Whether it happens, we'll just have to see, it's anyone's guess.
Congress said we can't take it down to zero. I don't want to project, I can't guess what will happen, but FDA does have authority.

Joy: Brazil has now banned menthol and the addition of sweeteners as of March this year. The WHO-FCTC has had tremendous success with this initiative. Will this action prompt FDA to speed up a similar ban on menthol and the addition of sweeteners beyond what we have seen with the FSPTC Act?

Dr. Kessler: We like to think that we are the leaders in public health, but what happens in other countries can affect the US. The FDA will need to base their decision on scientific literature, but just as we influence other countries, we do see other countries influence us.

Joy: During the process of my research..I should let you know that I work in the pharmaceutical industry, for Merck, and I have a particular interest in diabetes. In reviewing the various sweeteners, I was intrigued by the sugar pyrolysis within the burning cigarette, the carcinogens formed and the adverse effects seen on the beta cell via nicotine receptors within the pancreas. Typically, with cigarettes and diabetes, we talk about the micro vascular disease complications, but now the literature is looking at possible causation of diabetes.

Dr. Kessler: What kind of cells on the pancreas....the beta cells? Interesting.

Joy: Yes, the beta cells - which of course are responsible for insulin production.

Dr. Kessler: Certainly there is a whole world of nicotine and cardiovascular disease, and along with causing cancer, we know is #1 cause of MI in men...
I don’t think we fully understand the full effect of nicotine on cardiovascular disease and we see the consequences...many areas are still unexplained, and I

think you're right.... I wouldn’t be surprised if we find additional implications.

Joy: Throughout my research, my family has served as a sounding board for ideas....my daughter offered an interesting suggestion on an unadvertised gradual reduction in nicotine...i.e., incremental, but don't advertise that its happening to avoid a mutiny from the smokers.

Dr. Kessler: Well, people smoke for their nicotine...remember, nicotine is the driver. I gave a speech on this at one point, I can look for my notes, I don't have them with me...the law allows it.

Joy: I have to tell you...I have been married for 26 years, and my husband still smokes....although he says that he would quit, if the price of cigarettes goes too high....i.e.$100, so is there a price point that would convince most smokers to quit?

Dr. Kessler: I think that you will find that with young people especially, there is still lots of discretionary income, you can look up the literature, but you see a real relationship between price sensitivity, cost. You see a combination of effects , social norms where can you smoke and where can't you smoke all contribute.

Joy: Just thinking about GMP regulations....I read your book, which by the way now looks like an accordion with all of the pages turned down,... will we be able to capture the whole story....will it take a year to inspect each company?

Dr. Kessler: My sense is, not an attribution, industry knows a lot more about cigarette manufacturing than FDA does. This is a real difference from what we see with traditional Pharma GMP, because the Pharmaceutical companies set the standard with GMP and device, whereas the cigarette manufacturers know much more about their quality than the FDA does, it will take decades to learn. This is a law that will evolve over the next 20, 30, or 40 years, to learn more.

Joy: Does this somehow get tobacco companies off the hook, from a litigation standpoint, since now they can say that their products are FDA approved?

Dr. Kessler: We always knew we were running a risk with that...does this reinforce consumer confidence? At this point we need to establish.... there is much we don't know... use of reconstituted nicotine products and additives, the overall process, all will evolve, we don't understand as much as we need to, cigarettes are a highly engineered product.

Joy: When I read the chapter on your field investigations, I had a great visual from all of the road trips back from my early days as a pharmaceutical rep.....I was right there with Gary and Tom, through the tobacco fields of North Carolina and the long drives through no man's land and past the massive tobacco factories.

Dr. Kessler: These were interesting phases, we didn't know anything about manufacturing, for example how do we know how much or what kind of tobacco is actually going into a cigarette at this point.....

Joy: I like the concept of Electronic cigarettes,vaporizing nicotine, the FDA is not sure about how to regulate though.... some potential carcinogens seen with these as well... might be better to propose an overall ban on combustible nicotine.

Dr. Kessler: So the issue is, if you are Phillip Morris, what are you betting the future on, are there going to be other forms that work, I am not so sure, and I think you said it well, there may be safer alternatives, do you now see non-smokers take up these other products....can't outlaw combustible nicotine, no the law doesn't allow to go to zero, but can do an essence, like you said, what is sub therapeutic, like caffeine in coffee, no, I think there will be a set level that nicotine can be reduced to.

Joy: What if you restrict the purchase of cigarettes only to liquor stores, where you have to be at least 21 years old to even enter, combined with a higher price, similar to high priced liquors, fine wines?

Dr. Kessler: Depends on the new law's restriction on distribution. There is a lot to do under the existing law,and it will take decades.
I do think restricting access to liquor stores, and also make the price astronomical are good ideas, what about plain wrappers? Once you understand cue-induced wanting. Cue-induced wanting are triggers, such as time of day, location, all those are cues, that's more complicated, package, image, reduce the cues, this would be an important step to reduce the attractiveness. To the hard core smoker, may not be key. But consider addiction, ...cues. When you think about the First Amendment, especially issues in regards to Freedom of Speech, this is one area I am very interested in, how to legally impact, you need to do science to show color of pack, etc. are different considerations than ordinary speech because that's neutral. But visual cues that really trigger addictive behavior, are a different category of speech. This will be the big quest of the next decade, not all forms of speech should require the same degree of protection.

Joy: Will this be the topic of your next book?

Dr. Kessler: This is something I've always wanted to write on, one area I am interested in, cue induced wanting, can we regulate in a manner differently than, and not the same degree of protection as free speech? So, tell me what you are writing on, your thesis. I have an enormous respect for Gary, how else can I help you?

Joy: Thank you, Dr. Kessler. It has been tremendously helpful speaking with you today, and truly an honor. My thesis topic is on the historical politics of the FDA regulations of tobacco, mainly cigarettes, and I am pursuing a Master's Degree in Pharmacy, with an emphasis in Regulatory Affairs through the University of Georgia. Of course your book, and your regulatory efforts took up a whole chapter of my thesis. By the way, you had mentioned in your book that you still occasionally like to peruse the legacy online tobacco documents for updates, and perhaps I can help you here. The information that you had been trying to find on super critical extraction has recently been posted, in one of the last updates. I just saw several documents posted on this.

Dr. Kessler: Perfect! Thanks. So it sounds like you are already done with your thesis, what did you conclude with your paper?

Joy: I concluded that throughout history, the regulatory issues which prevented cigarettes from FDA jurisdiction were heavily influenced by the cigarette industry lobbying efforts. It's a shame that even with the best of scientific evidence to support your case, there were political and historical reasons that prevented it from happening. I also concluded that although the FSPTC Act has now given the FDA the authority that it needs, the tobacco industry is still influencing the speed at which any substantial action is taken.

Dr. Kessler: How do you think the new Center For Tobacco is doing?

Joy: They seem to be moving rather slowly. I talked about this in my paper. We already have Brazil banning menthol and all sweeteners, where our TPSAC is still back at the office having meetings to take another look at the data, for over three years now .....it is almost time for this group to rotate off of the panel, so the new team will have to be brought up to speed again, which probably means even more delays in seeing any action. The list of sweeteners we are banning will only affect less than 1% of cigarettes, vs. the 40% which could be affected by a menthol ban. And an even greater percentage would benefit from a complete ban of all sweeteners so that the harmful carcinogens wouldn't be so easily inhaled.

Dr. Kessler: When sugars undergo pyrolysis, there are thousands of harmful chemicals given off....I forget the main ones in this reaction.

Joy: Acetylaldehydes mostly, PAH compounds , all carcinogens.
Dr. Kessler: I am going to have to run – please let me know if there is anything else. Please also give my best to Gary.
Joy: Thank you, Dr. Kessler – I really appreciate you taking the time to speak with me, and please pass along my thanks to Paulette.
Dr. Kessler: Thanks, will do. Take care now.

APPENDIX F: WHO FCTC

Signatories to the WHO FCTC: **168**
Parties to the WHO FCTC: **176** (entry into force for Czech Republic: 30 August 2012)

Participant	Signature date *(day-month-year)*	Ratification, Acceptance (A), Approval (AA), Formal confirmation (c), Accession (a), Succession (d) *(day-month-year)*	Entry into force *(day-month-year)*
Afghanistan	29/06/2004	13/08/2010	11/11/2010
Albania	29/06/2004	26/04/2006	25/07/2006
Algeria	20/06/2003	30/06/2006	28/09/2006
Angola	29/06/2004	20/09/2007	19/12/2007
Antigua and Barbuda	28/06/2004	05/06/2006	03/09/2006
Argentina	25/09/2003		
Armenia		29/11/2004 a	27/02/2005
Australia	05/12/2003	27/10/2004	27/02/2005
Austria	28/08/2003	15/09/2005	14/12/2005
Azerbaijan		01/11/2005 a	30/01/2006
Bahamas	29/06/2004	03/11/2009	01/02/2010
Bahrain		20/03/2007 a	18/06/2007
Bangladesh	16/06/2003	14/06/2004	27/02/2005
Barbados	28/06/2004	03/11/2005	01/02/2006
Belarus	17/06/2004	08/09/2005	07/12/2005
Belgium	22/01/2004	01-11-2005	30/01/2006
Belize	26/09/2003	15/12/2005	15/03/2006
Benin	18/06/2004	03/11/2005	01/02/2006
Bhutan	09/12/2003	23/08/2004	27/02/2005
Bolivia (Plurinational State of)	27/02/2004	15/09/2005	14/12/2005
Bosnia and Herzegovina		10/07/2009	08/10/2009
Botswana	16/06/2003	31/01/2005	01/05/2005
Brazil	16/06/2003	03/11/2005	01/02/2006
Brunei Darussalam	03/06/2004	03/06/2004	27/02/2005

Participant	Signature date *(day-month-year)*	Ratification, Acceptance (A), Approval (AA), Formal confirmation (c), Accession (a), Succession (d) *(day-month-year)*	Entry into force *(day-month-year)*
Bulgaria	22/12/2003	07/11/2005	05/02/2006
Burkina Faso	22/12/2003	31/07/2006	29/10/2006
Burundi	16/06/2003	22/11/2005	20/02/2006
Cambodia	25/05/2004	15/11/2005	13/02/2006
Cameroon	13/05/2004	03/02/2006	04/05/2006
Canada	15/07/2003	26/11/2004	27/02/2005
Cape Verde	17/02/2004	04/10/2005	02/01/2006
Central African Republic	29/12/2003	07/11/2005	05/02/2006
Chad	22/06/2004	30/01/2006	30/04/2006
Chile	25/09/2003	13/06/2005	11/09/2005
China[1]	10/11/2003	11/10/2005	09/01/2006
Colombia		10/04/2008 a	09/07/2008
Comoros	27/02/2004	24/01/2006	24/04/2006
Congo	23/03/2004	06/02/2007	07/05/2007
Cook Islands	14/05/2004	14/05/2004	27/02/2005
Costa Rica	03/07/2003	21/08/2008	19/11/2008
Cote d'Ivoire	24/07/2003	13/08/2010	11/11/2010
Croatia	02/06/2004	14/07/2008	12/10/2008
Cuba	29/06/2004		
Cyprus	24/05/2004	26/10/2005	24/01/2006
Czech Republic	16/06/2003	01/06/2012	30/08/2012
Democratic People's Republic of Korea	17/06/2003	27/04/2005	26/07/2005
Democratic Republic of the Congo	28/06/2004	28/10/2005	26/01/2006
Denmark[2]	16/06/2003	16-12-2004	16/03/2005
Djibouti	13/05/2004	31/07/2005	29/10/2005
Dominica	29/06/2004	24/07/2006	22/10/2006
Ecuador	22/03/2004	25/07/2006	23/10/2006
Egypt	17/06/2003	25/02/2005	26/05/2005
El Salvador	18/03/2004		
Equatorial Guinea		17/09/2005 a	16/12/2005

Participant	Signature date *(day-month-year)*	Ratification, Acceptance (A), Approval (AA), Formal confirmation (c), Accession (a), Succession (d) *(day-month-year)*	Entry into force *(day-month-year)*
Estonia	08/06/2004	27/07/2005	25/10/2005
Ethiopia	25/02/2004		
European Community	16/06/2003	30/06/2005 c	28/09/2005
Fiji	03/10/2003	03/10/2003	27/02/2005
Finland	16/06/2003	24/01/2005	24/04/2005
France	16/06/2003	19/10/2004 AA	27/02/2005
Gabon	22/08/2003	20/02/2009	21/05/2009
Gambia	16/06/2003	18/09/2007	17/12/2007
Georgia	20/02/2004	14/02/2006	15/05/2006
Germany	24/10/2003	16/12/2004	16/03/2005
Ghana	20/06/2003	29/11/2004	27/02/2005
Greece	16/06/2003	27/01/2006	27/04/2006
Grenada	29/06/2004	14/08/2007	12/11/2007
Guatemala	25/09/2003	16/11/2005	14/02/2006
Guinea	01/04/2004	07/11/2007	05/02/2008
Guinea-Bissau		07/11/2008 a	05/02/2009
Guyana		15/09/2005 a	14/12/2005
Haiti	23/07/2003		
Honduras	18/06/2004	16/02/2005	17/05/2005
Hungary	16/06/2003	07/04/2004	27/02/2005
Iceland	16/06/2003	14/06/2004	27/02/2005
India	10/09/2003	05/02/2004	27/02/2005
Iran (Islamic Republic of)	16/06/2003	06/11/2005	04/02/2006
Iraq	29/06/2004	17/03/2008	15/06/2008
Ireland	16/09/2003	07/11/2005	05/02/2006
Israel	20/06/2003	24/08/2005	22/11/2005
Italy	16/06/2003	02/07/2008	30/09/2008
Jamaica	24/09/2003	07/07/2005	05/10/2005
Japan	09/03/2004	08/06/2004 A	27/02/2005
Jordan	28/05/2004	19/08/2004	27/02/2005
Kazakhstan	21/06/2004	22/01/2007	22/04/2007

Participant	Signature date *(day-month-year)*	Ratification, Acceptance (A), Approval (AA), Formal confirmation (c), Accession (a), Succession (d) *(day-month-year)*	Entry into force *(day-month-year)*
Kenya	25/06/2004	25/06/2004	27/02/2005
Kiribati	27/04/2004	15/09/2005	14/12/2005
Kuwait	16/06/2003	12/05/2006	10/08/2006
Kyrgyzstan	18/02/2004	25/05/2006	23/08/2006
Lao People's Democratic Republic	29/06/2004	06/09/2006	05/12/2006
Latvia	10/05/2004	10/02/2005	11/05/2005
Lebanon	04/03/2004	07-12-2005	07/03/2006
Lesotho	23/06/2004	14/01/2005	14/04/2005
Liberia	25/06/2004	15/09/2009	14/12/2009
Libya	18/06/2004	07/06/2005	05/09/2005
Lithuania	22/09/2003	16/12/2004	16/03/2005
Luxembourg	16/06/2003	30/06/2005	28/09/2005
Madagascar	24/09/2003	22/09/2004	27/02/2005
Malaysia	23/09/2003	16/09/2005	15/12/2005
Maldives	17/05/2004	20/05/2004	27/02/2005
Mali	23/09/2003	19/10/2005	17/01/2006
Malta	16/06/2003	24/09/2003	27/02/2005
Marshall Islands	16/06/2003	08/12/2004	08/03/2005
Mauritania	24/06/2004	28/10/2005	26/01/2006
Mauritius	17/06/2003	17/05/2004	27/02/2005
Mexico	12/08/2003	28/05/2004	27/02/2005
Micronesia (Federated States of)	28/06/2004	18/03/2005	16/06/2005
Mongolia	16/06/2003	27/01/2004	27/02/2005
Montenegro[3]		23/10/2006 d	21/01/2007
Morocco	16/04/2004		
Mozambique	18/06/2003		
Myanmar	23/10/2003	21/04/2004	27/02/2005
Namibia	29/01/2004	07/11/2005	05/02/2006
Nauru		29/06/2004 a	27/02/2005
Nepal	03/12/2003	07/11/2006	05/02/2007
Netherlands	16/06/2003	27/01/2005 A	27/04/2005

Participant	Signature date *(day-month-year)*	Ratification, Acceptance (A), Approval (AA), Formal confirmation (c), Accession (a), Succession (d) *(day-month-year)*	Entry into force *(day-month-year)*
New Zealand[4]	16/06/2003	27/01/2004	27/02/2005
Nicaragua	07/06/2004	09/04/2008	08/07/2008
Niger	28/06/2004	25/08/2005	23/11/2005
Nigeria	28/06/2004	20/10/2005	18/01/2006
Niue	18/06/2004	03/06/2005	01/09/2005
Norway	16/06/2003	16/06/2003 AA	27/02/2005
Oman		9/03/2005 a	07/06/2005
Pakistan	18/05/2004	03/11/2004	27/02/2005
Palau	16/06/2003	12/02/2004	27/02/2005
Panama	26/09/2003	16/08/2004	27/02/2005
Papua New Guinea	22/06/2004	25/05/2006	23/08/2006
Paraguay	16/06/2003	26/09/2006	25/12/2006
Peru	21/04/2004	30/11/2004	28/02/2005
Philippines	23/09/2003	06/06/2005	04/09/2005
Poland	14/06/2004	15/09/2006	14/12/2006
Portugal	09/01/2004	08/11/2005 AA	06/02/2006
Qatar	17/06/2003	23/07/2004	27/02/2005
Republic of Korea	21/07/2003	16/05/2005	14/08/2005
Republic of Moldova	29/06/2004	3/02/2009 a	04/05/2009
Romania	25/06/2004	27/01/2006	27/04/2006
Russian Federation		03/06/2008 a	01/09/2008
Rwanda	02/06/2004	19/10/2005	17/01/2006
Saint Kitts and Nevis	29/06/2004	21/06/2011	19/09/2011
Saint Lucia	29/06/2004	07/11/2005	05/02/2006
Saint Vincent and the Grenadines	14/06/2004	29/10/2010	27/01/2011
Samoa	25/09/2003	03/11/2005	01/02/2006
San Marino	26/09/2003	07/07/2004	27/02/2005
Sao Tome and Principe	18/06/2004	12/04/2006	11/07/2006
Saudi Arabia	24/06/2004	09/05/2005	07/08/2005
Senegal	19/06/2003	27/01/2005	27/04/2005
Serbia	28/06/2004	08/02/2006	09/05/2006

Participant	Signature date *(day-month-year)*	Ratification, Acceptance (A), Approval (AA), Formal confirmation (c), Accession (a), Succession (d) *(day-month-year)*	Entry into force *(day-month-year)*
Seychelles	11/09/2003	12/11/2003	27/02/2005
Sierra Leone		22/05/2009	20/08/2009
Singapore	29/12/2003	14/05/2004	27/02/2005
Slovakia	19/12/2003	04/05/2004	27/02/2005
Slovenia	25/09/2003	15/03/2005	13/06/2005
Solomon Islands	18/06/2004	10/08/2004	27/02/2005
South Africa	16/06/2003	19/04/2005	18/07/2005
Spain	16/06/2003	11/01/2005	11/04/2005
Sri Lanka	23/09/2003	11/11/2003	27/02/2005
Sudan	10/06/2004	31/10/2005	29/01/2006
Suriname	24/06/2004	16/12/2008	16/03/2009
Swaziland	29/06/2004	13/01/2006	13/04/2006
Sweden	16/06/2003	07/07/2005	05/10/2005
Switzerland	25/06/2004		
Syrian Arab Republic	11/07/2003	22/11/2004	27/02/2005
Thailand	20/06/2003	08/11/2004	27/02/2005
The former Yugoslav Republic of Macedonia		30/06/2006 a	28/09/2006
Timor-Leste	25/05/2004	22/12/2004	22/03/2005
Togo	12/05/2004	15/11/2005	13/02/2006
Tonga	25/09/2003	08/04/2005	07/07/2005
Trinidad and Tobago	27/08/2003	19/08/2004	27/02/2005
Tunisia	22/08/2003	07/06/2010	05/09/2010
Turkey	28/04/2004	31/12/2004	31/03/2005
Turkmenistan		13/05/2011	11/08/2011
Tuvalu	10/06/2004	26/09/2005	25/12/2005
Uganda	05/03/2004	20/06/2007	18/09/2007
Ukraine	25/06/2004	06/06/2006	04/09/2006
United Arab Emirates	24/06/2004	07/11/2005	05/02/2006
United Kingdom of Great Britain and Northern Ireland	16/06/2003	16/12/2004	16/03/2005
United Republic of Tanzania	27/01/2004	30/04/2007	29/07/2007

Participant	Signature date *(day-month-year)*	Ratification, Acceptance (A), Approval (AA), Formal confirmation (c), Accession (a), Succession (d) *(day-month-year)*	Entry into force *(day-month-year)*
United States of America	10/05/2004		
Uruguay	19/06/2003	09/09/2004	27/02/2005
Uzbekistan		15/05/2012	13/08/2012
Vanuatu	22/04/2004	16/09/2005	15/12/2005
Venezuela (the Bolivarian Republic of)	22/09/2003	27/06/2006	25/09/2006
Viet Nam	03/09/2003	17/12/2004	17/03/2005
Yemen	20/06/2003	22/02/2007	23/05/2007
Zambia		23/05/2008 a	21/08/2008

Reference: http://www.who.int/fctc/signatories_parties/en/index.html

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The treatment of schizophrenia isn't the only positive effect that nicotine has on the brain. A series of very interesting studies from multiple academic sources confirms that the **risk of Parkinson's disease and Alzheimer's disease is surprisingly higher in non-smokers than in smokers**. Doctor Laura Fratiglioni of Huddinge University Hospital in Sweden states, "Cigarette smokers are 50% less likely to have PD or AD than are age and gender-matched nonsmokers [...] cigarette smoking exerts an undefined, biologic, neuroprotective influence against the development of PD and AD."
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739 (2d Cir. 1969) (describing other relevant sources of manufacturer intent); Alberty Food Prods. v. United States, 194 F.2d 463 (9th Cir. 1952) (same).

[145] Judge Friendly, for example, in a case that considered whether certain vitamin and mineral supplements should be classified as drugs, found that the FDA was not bound by a manufacturerôs subjective claims but could also make use of such ñobjective evidenceò as consumer use. Natôl Nutritional Foods Assôn v. FDA, 504 F.2d 761, 789 (2d Cir. 1974).
Therapeutic use, however, had to ñ far outweighò other uses in order to count as objective evidence for drug classification. Natôl Nutritional Foods Assôn v. Mathews, 557 F.2d 325, 336 (2d Cir. 1977).
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[161] Ibid#131, p.132.
[162] Ibid#131, at 143-44, 152-53.
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[164] Ibid#131, p.152; see also Jurisdictional Statement, *supra* note 37, at 45,067-75 (noting the Agencyôs grounds for contesting the industryôs position on the tar-to-nicotine ratio) and Jurisdictional Statement, *supra* note 37, at 45,068-69.
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[170] Ibid#131,304-306.
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