8-2020

Evaluation of the Premarket Tobacco Product Application for Electronic Cigarettes

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by

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A Thesis Submitted in Partial Fulfillment of the Requirement for the Degree of Master of Science in Science, Technology, and Public Policy

Department of Public Policy
College of Liberal Arts

Rochester Institute of Technology
Rochester NY
August 2020

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A thesis proposal submitted to the
Public Policy Program at
Rochester Institute of Technology
in partial fulfillment of The Science,
Technology & Public Policy
Masters Degree

by **Maya Lara**

under the faculty guidance of

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August 2020

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ABSTRACT

Use of tobacco has remained one of the most lethal pastimes within the United States. With the creation of new products, like electronic cigarettes (e-cigarettes), more and more individuals have begun to engage in this activity. In 2019, an epidemic surrounding the use of e-cigarettes emerged causing a multitude of users to suffer harmful respiratory illnesses. These events triggered the need for further investigation not only into the research used to analyze e-cigarettes, but also the regulation process used to validate them. E-cigarettes, like their predecessor traditional cigarettes, are regulated by the Center for Tobacco Products (CTP) within the United States Food and Drug Administration (FDA). Through premarket tobacco product applications (PMTA), the CTP determines whether tobacco products are safe for public use. This thesis was used to investigate whether the current regulatory process is able to effectively analyze all of the risks and health implications associated with the use of e-cigarettes. After reviewing research from literature to define the current state of knowledge surrounding the health impacts of e-cigarettes, an applied case study was conducted to determine whether the research in the PMTA was sufficient in assessing the safety of these devices. The findings of this research reveal that although the PMTA included some of the important research areas found in the literature review, its analysis was limited due to the continuous reliance on the comparison of e-cigarettes and traditional cigarettes to validate the argument of safety.

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CHAPTER 1: INTRODUCTION

Within the United States, the use of tobacco remains one of the most hazardous recreational activities, resulting in over 480,000 preventable deaths per year (Centers for Disease Control and Prevention [CDC], n.d.a). Since their creation in the 19th century, traditional cigarettes have steadily increased in popularity throughout society ("History of Tobacco", n.d.). Although they remain popular, traditional cigarettes are only one type of tobacco product. Other tobacco products on the market include: cigars, snuff, chewing tobacco, hookah, and most recently electronic cigarettes (e-cigarettes). The creation of these devices classified as e-cigarettes or electronic nicotine delivery system (ENDS) has introduced a rapidly expanding market, especially in the United States. The users of e-cigarette devices are comprised of not only adults, but also children. In 2018, the United States Food and Drug Administration (FDA) noted that 3.62 million middle and high school students are e-cigarettes users and in 2019, this same number escalated to 5 million. (U.S. Food and Drug Administration [FDA], n.d.e, n.d.d).

Although e-cigarettes have been approved by the Center for Tobacco Products (CTP) within the U.S. Food and Drug Administration (FDA), emerging evidence has revealed that these devices are potentially more hazardous than previously publicized (Knowles and Sun, 2019). Little research has been done to accurately assess all of the health effects, both short- and long-term, of these devices (Sharpless, 2019.) Specifically, no research has been done to evaluate the potential negative health effects caused by the ingredients in e-cigarette liquids. For example, although deemed safe by the FDA, propylene glycol, a compound commonly used in e-cigarette liquids (e-liquids), was only researched for use in topical, oral, and injectable consumer products (Cobb and Abrams, 2011). Since the e-liquids change from liquid to vapor, inhaling propylene

glycol could stimulate alternative effects from those previously seen in the research of approved consumer products.

There is a vast amount of variability amongst types of e-cigarettes. Currently, e-cigarettes are classified by their product design; some resemble USB flash drives, while others resemble pens. Diversity of design, however, is not the only variable factor within these devices. There are a multitude of ingredients that make up the e-liquids used in e-cigarettes. In 2014, there were not only 466 different brands of e-cigarettes, but also 7764 distinctive flavors being sold online (Zhu et al., 2014). The addition of flavors creates vast differences, particularly, in the concentration of nicotine being used in the formulas. Although the ability to modify and customize e-cigarettes is commonly used as a marketing ploy by companies to increase the sale of their products (Zhu et al., 2014), the diversity of e-cigarettes also warrants questions surrounding both the risks to e-cigarette users and the efficacy of the regulation process in analyzing these devices. These modifications could potentially impact both the function and the use of the device, which could alter how they should be analyzed.

Recently, there has been an abundance of events surrounding the development of respiratory illnesses in e-cigarettes users. Many individuals have succumbed to acute respiratory distress syndrome, a life-threatening condition caused by the accumulation of fluid in the lungs, which obstructs the circulation of oxygen in the bloodstream (Knowles and Sun, 2019), preventing the

body from functioning properly. The latest outbreak information indicates that there has been almost 1479 e-cigarette associated respiratory injury cases and 33 confirmed deaths (CDC, n.d.d).

Due to the rising number of cases, state officials have taken legislation of e-cigarettes into their own hands, allowing them to decrease the regulatory void created by the indolence of the federal government ("Outbreak of Lung Injury", n.d.). Michigan, for instance, was the first of many states to create e-cigarette legislation. The state government limited the sale of e-cigarettes by placing an emergency ban on all flavors other than tobacco. In February of 2020, the resident officially enacted a federal ban on the flavored e-cigarette products.

The overall goal of this thesis is to determine whether the regulatory process for e-cigarettes allows for effective review of the safety of e-cigarettes. The thesis will focus on one of the only Premarket Tobacco Product Applications available to the public. By evaluating the content in the PTMA, I will be able to examine what characteristics are included when assessing the harmfulness of e-cigarettes and determine whether the evaluation of these characteristics is sufficient by comparing them research found within the broader academic literature. I will also identify any areas were overlooked or ignored within the substantial review process.

CHAPTER 2: RESEARCH QUESTIONS

There is a lot of variation between cigarettes not only in their design, but also in their auxiliary components, like e-liquids. Although substantial equivalence can be used to show that a device is similar to an already marketed device, how do we know whether the disparity between the devices does not have hazardous health consequences? Of the 302 applications submitted during the 2019 fiscal year, 296 applications were submitted through the substantial equivalence pathway (FDA, n.d.a). If there is a comparison being made, between electronic cigarettes or even traditional cigarettes, then what are areas the of research being used to examine their similarities?

The research of this thesis focuses on the regulation of e-cigarettes. In 2019, there was not only a large growth in the number of youth users, but also a large number of individuals who became impaired, even hospitalized, due to their use of these products. Through regulation, these devices were able to receive a marketing order, which means that they were proposed to be safe for the public. In order to create a solution, we have to determine where the problem occurs. Thus, the process of regulating these devices needs to be analyzed in order to determine what factors inhibited the regulation process from uncovering the health problems associated with the device. The research within this thesis surrounds two large questions:

- Is the evidence provided in PTMAs adequate to claim substantial equivalence?
- Has the Premarket Tobacco Product Applications (PTMA) been effective in the regulation of e-cigarettes?

The first question looks at the information that companies provide within their PMTA. I will look at what scientific research companies supply for the Substantive Review phase of the PMTA process. This will allow me to examine the findings of their research, assess the quality of

research, and compare their findings with the literature. From this information, I cannot only determine what evidence is provided, but also whether it is substantial in the analysis of e-cigarette devices.

The second question surrounds the one of the main functions of the Family Smoking Prevention and Tobacco Control Act (FSPTCA), which is to create a process that effectively regulates e-cigarettes, a type of tobacco product. To determine the effectiveness of the process, we have to determine whether the research included in the PMTA incorporate all of the areas important in analyzing the devices. Important areas will be determined decided by the areas that are identified as important in academic literature.

CHAPTER 3: BACKGROUND

Beginning in the 1960s, there has been a multitude of policy measures that have impacted both the advertisement and use of tobacco products. From the Federal Cigarette Labeling and Advertising Act of 1965 to the Public Health Cigarette Smoking Act of 1969, tobacco products have been a controversial topic within legislature (Centers for Disease Control and Prevention, n.d.c). In 2009, President Barack Obama gave the FDA the ability to regulate tobacco products through the creation of the Family Smoking Prevention and Tobacco Control Act (FSPTCA) under the Food, Drug, and Cosmetic Act. In addition to producing standards for tobacco products, the FDA can require companies to disclose both the contents of their products and the research used to evaluate their health effects (Public Health Center, n.d.).

Before being placed on the market, "new tobacco products" have to receive a tobacco product marketing order from the FDA. "New tobacco products" are defined as tobacco products that were not commercially marketed before February 15, 2007. In order to receive approval, companies can go through three different pathways: submitting of a premarket tobacco product applications (PMTA), demonstrating substantial equivalence, or requesting an exemption from substantial equivalence. These applications allow the FDA to assess the benefits and risks of the product on public, both users and non-users (FDA, n.d.c). Therefore, all tobacco products, including e-cigarettes must go through this regulatory process, as shown in Figure 1.

Figure 1: The six steps of the FDA regulatory process for PMTA (FDA, n.d.c).

The process begins with a Presubmission Meeting, an optional meeting between the company and the Center for Tobacco Products (CTP) where the company can receive guidance and assistance regarding their plans prior to submitting the PMTA. After the submission of the PMTA, the CTP conducts an Acceptance Review to confirm whether the product falls under its jurisdiction. Following the Acceptance Review, the Filing Review phase is used to verify that the PMTA includes all the necessary items. This thesis is focused on the step that succeeds the Filing Review, the Substantive Review. Substantive Review determines whether companies will receive a marketing order letter for their device which is officially granted in the Action phase of the process. Substantive Review is the phase where the CTP examines the scientific research that was submitted within the PMTA and provides recommendations. Within this step, the scientific research is used to provide evidence showing the health-related effects related to the tobacco product, allowing the CTP to assess its safety. Postmarket Reporting is the last phase of the process. After receiving a marketing letter, the FDA requires companies to keep information on the product.

E-cigarettes are battery operated devices classified by their ability to heat liquids into aerosols, a mixture of liquid or solid particles in a gas. Initially, in 2011, the FDA wanted to regulate electronic cigarettes as drug delivery devices. However, since there were no therapeutic claims surrounding the devices, the courts denied their request and required e-cigarettes to be regulated as tobacco products citing the FSPTCA as the reason for the ruling (Cobb and Abrams, 2011). The first e-cigarette was created in the 1960s, when Hebert A. Gilbert submitted a patent for a ‘smokeless nontobacco cigarette’, an alternative to smoking cigarettes (U.S. Department of Health and Human Services et al., 2016, p.10). E-cigarettes have four common pieces within their design: a power source, a heating element, a pressure switch, and a battery. First generation

e-cigarettes are classified by their likeness to traditional cigarettes. These devices resemble both the look and the feel of traditional cigarettes, becoming an alternative for smoking. Second generation e-cigarettes are devices characterized by two elements, an atomizer or thin battery, and a clearomizer, a clear cartridge that holds the e-liquids ("E-cigarette Devices, Uses", 2018). Unlike the first two generations, third generation e-cigarettes bear no resemblance to traditional cigarettes. They are classified by the ability of their parts to be customizable, replaceable, and refillable.

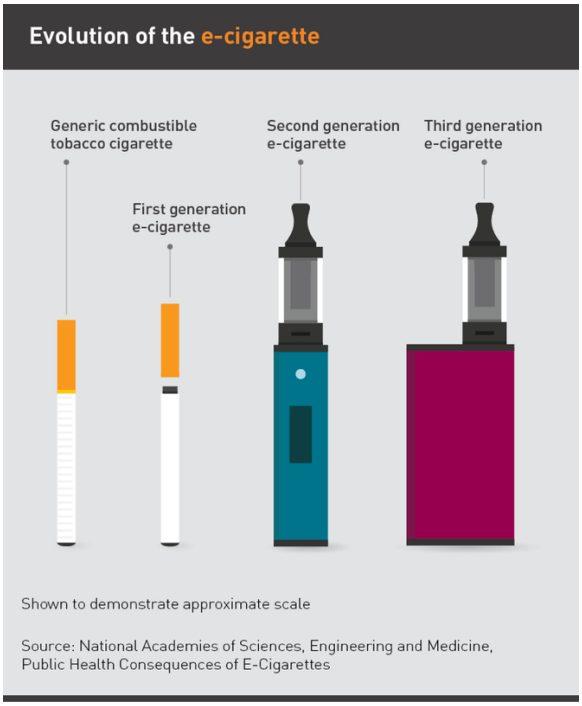

Figure 2: The image above illustrates the differences between the various generation of e-cigarettes (Truth Initiative, 2019).

The main difference between e-cigarettes and traditional cigarettes is the absence of tobacco in e-liquids. Unlike traditional cigarettes, e-cigarettes contain nicotine, an addictive substance found in tobacco. Products like e-cigarettes and other non-smokable products are perceived to be less harmful by the public not only because they have lower concentrations of

harmful chemicals, but also because they do not rely on combustion (Pepper et al., 2014). Although the ingredients within the e-liquid, for instance nicotine, are less concentrated, they still have deleterious effects. Diseases associated with smoking traditional cigarettes, like lung cancer and emphysema, develop after years of constant smoking. Recent events, however, have shown that damage to the lungs can occur in less than a year ("Is Vaping Safer than", 2019). Table 1 lists some of the ingredients mentioned by the American Lung Association that are typically found in e-cigarettes.

Table 1: List of Ingredients in e-cigarettes compiled from American Lung Association.

Ingredients	**Uses**
Propylene glycol	Common food additive. Used to make antifreeze and paint solvent.
Acrolein	Herbicide used to kill weeds
Diacetyl	Chemical linked to bronchiolitis obliterans (popcorn lung)
Benzene	Volatile compound found in car exhaust
Cadmium	Toxic metal linked with breathing problems and disease

CHAPTER 4: METHODS

The methods of the thesis can be separated into two parts, the methods for the literature review and the methods used to find the premarket tobacco product applications (PMTA).

Literature Review

The information gathered within this literature review is separated into three different categories: various generations of e-cigarettes, the comparison of e-cigarettes to traditional cigarettes, and the comparison of the materials in both e-liquids and aerosols. To find materials, two different databases, google scholar and RIT library were utilized. The search terms include: *"health e-cigarettes", "chemicals in e-cigarettes", "chemical in e-cigarettes", "e-cigarette flavor compounds", "first generation e-cigarettes", "second generation e-cigarettes", "third generation e-cigarettes"* and *"traditional and e-cigarettes".* Through the multiple searches, seventy papers were found.

Since the material within this literature review was being used to identify important research, it was imperative that they were experimental research that looked at the health effects associated with e-cigarettes. Many of the documents that came back were patents of e-cigarettes and news articles of current events. Patents were excluded from this review because although they illustrate the versatility in design, patents are unable to show whether the design of e-cigarettes impacts the health of its users. News articles provide good background information, but they do not provide data in relation to the scientific analysis of e-cigarettes. They can account for what injuries are frequent amongst users, but they cannot show the relationship between what is causing these health-related issues; thus, they were also excluded from this literature review. Other research that was excluded includes research that focused only on defining the differences

without discussing the impact on health. The absence of health impact would not allow this paper to gather enough information about the implications that versatility could potentially have on health. After refining the search criteria, twenty-seven papers were selected to provide data that would allow me to find ideas that were prevalent amongst different areas of research.

Applied Case Study

Locating the premarket tobacco product applications was a difficult task. The Food and Drug Administration, which is made up of several centers, had a lot of information that on its website. I had to use the FDA search for the information that I was hoping to acquire. After locating the applications with the 'premarket tobacco application' search term, I was able to examine applications using the seventh link titled, "Premarket Tobacco Product Marketing Order" (FDA, n.d.b). The page listed marketing orders for PMTAs from two separate years, 2015 or 2019. Within these two years, there was a total of four PMTAs e-cigarette devices, however, they were all under the 2019 fiscal year and submitted by one company, Phillip Morris S.A. (FDA, n.d.b).

Since the analysis of this thesis relied heavily on the details of the PMTA, the acquisition of these documents was a sizable limitation. I did not want to rely solely on a few PMTAs, especially since they were all submitted by a single company. In order to rectify the situation, I attempted to obtain more applications. Initially, I reached out to several individuals and departments associated with the FDA through email and phone to initiate correspondence about finding additional PMTAs, however, I was not able to find more information through this route. The information provided by these sources referred me back to information I already acquired when searching the FDA website. In addition to this, through the help of my advisor, I was able

to use a resource called MuckRock. Through the Freedom of Information Act, MuckRock is able to assist individuals in gathering government documents. Through this platform, I requested to see e-cigarette PMTAs from 2018, however this request was denied. In March, I received a response, located in appendix 1, which noted that the existence of PMTAs could neither confirmed nor denied, referencing "Extemption 4 of the FOIA and 21 CFR 20.61 (b)(c)" (appendix 1).

Since I was unable to acquire additional PMTAs, I was restricted to the four applications submitted by Phillip Morris S.A that I located on the FDA website. These four applications were based on the flavor of the heatsticks (3) that were used in the devices and the actual system. Under closer examination, I found that there were no major differences between them and that they all included similar information and research. Thus, I chose to focus on one of the applications for this thesis. The specific application analyzed was the first of the four applications located on the 'Premarket Tobacco Product Marketing Order' page under the PMTAs for the 2019 fiscal year, titled 'PM0000424', associated with the Marlboro Menthol Heatsticks.

The PMTA was organized in five different sections: Executive Summary, Review of PMTA, Product Labeling, Consumer Comprehension, & Marketing Plan, and Conclusions & Recommendations (FDA, 2019, p. 6-7). The second section, Review of PMTA, contained three subsections that focused on the experimental research done to analyze the device. The three sub-sections were: Toxicological Risk Assessment, Behavioral & Clinical Pharmacological Assessment, and Individual Health Impact. Although these sections contained information about the experiments, they mostly were a summary of the experiments and commentary from

individuals from the CTP. For example, most of the quantitive data was excluded from the PMTA.

To develop a clearer understanding of the evidence, I attempted to find the documentation of the actual experiments. Three experiments were found by using the experimental numbers that were referenced within the PMTA. The first experiment, which focused on smoking topography was referenced as *'ZRHM-REXA-08'*. The next experiment, referenced by *'ZRHM-PK-06-US'*, was focused on pharmacokinetics. The final experiment number, *'RLS-ZRH-2015-249*, included details about all of the in vivo experiments that focused on aerosol toxicity.

To find the detailed information about the experiments executed in the PMTA, a google search was conducted using the experimental number with the addition of the search term *'pmiscience'*. For example, for the data for the smoking topography was found using the search term '*ZRHM-REXA-08 pmiscience'*. There were some redactions within PMI science documents, however, they did not take away from the data or the findings of the experiments.

Analysis

Gathering and organizing the scientific research collected was an immense portion of this thesis. The first analysis was conducted during the literature review, resulting in the definition of the important research areas for e-cigarettes. These areas helped to organize the research of the PMTA into three sections: Smoking Topography, the Pharmacological Assessment of Nicotine, and Aerosol Toxicity. From the experimental research of the experiments within the PMTA, each experiment was detailed to develop of an understanding of what was done and to learn the findings. In addition to defining the research areas, the research from the literature review was used for a comparison. The findings from those papers were compared to the experiments

conducted within the PMTA. In addition to the comparison between the research, the findings were organized by their potential for health impact by denoting them as ‘low’, ‘medium’, and ‘high’. This was used to help categorize the information establishing a correlation with importance. High health impact implies that it there is a high importance when assessing the health effects during the analysis of these devices. The results of the research comparisons thesis allowed for evaluation into the effectiveness of e-cigarette regulation.

CHAPTER 5: FINDINGS

Findings can be broken in three sections: research areas within literature important in evaluating e-cigarettes, experimental areas included within the premarket tobacco product application (PMTA), and the assessment of research quality within the Pre-market tobacco application. In addition to showing the importance of different e-cigarette areas that are researched, I will also make several comparisons between what is shown in literature, what is provided in the PMTA, ultimately, determining whether the evidence provided in the PMTA is substantial enough to be considered safe for consumers.

I will review my findings, starting with a review of areas and ideas that are critical when analyzing the health effects of e-cigarettes. After defining these research areas, I will use them to organize the experiments of the PMTA and see what evidence, if any, was provided. Following the discussion surrounding the findings of each experiments, I will then compare the findings of research used in the literature review to the findings of the PMTA. Finally, I will assess the quality of data included in the PMTA.

CHAPTER 5A: AREAS THAT IMPACT SMOKING (LITERATURE REVIEW)

Within the literature, research areas are able to provide evidence about what should be considered when evaluating electronic cigarettes. In order to be considered safe and receive a marketing order, tobacco products, like e-cigarettes, have to be tested to show the effects associated with their usage. Both harmless and hazardous effects should be considered because they play a role in the assessment of risks that consumers could potentially encounter. When there is consistency between findings of research, it allows the importance of that subject area to be emphasized. For instance, if the majority of research made claims that smoking behavior is different in e-cigarettes, then the research within the PMTA should include research that examines smoking behavior.

Findings do not always agree between research. This does not mean, however, that these research areas are insignificant. Contrasts between findings in research show not only inconsistencies between research, but also the need for further research in these areas. These areas are also important in showing the risks of these e-cigarettes. Including these research areas would be valuable addition to the regulatory process so that it could ensure that its review of these devices is truly comprehensive.

Within the three categories below, a variety of research was used to examine the different ideas and whether they were consistent. The three main focuses of the papers are the comparison of the various generations of e-cigarettes, the comparison of e-cigarettes to traditional cigarettes, and the comparison of the materials in both e-liquids and aerosols. These comparisons help to identify areas that are necessary in assessing the harmfulness of the e-cigarettes.

Electronic versus Traditional Cigarettes

Electronic and traditional cigarettes differ, especially in their usage. Eight papers were used to develop the comparisons of this section. The papers within this section are limited. Four of the papers only look at the short-term effects cause by the usage of e-cigarettes. Although the other papers were not classified as having a short-term evaluation of health effects, their time periods of evaluation were still short in comparison to the period it takes for noticing a different in health effects. The longest evaluation time within this section which occurred in the study conducted by Harrington, Cheong, Hendricks, and Kohler (2015) was 6 months. The most common idea throughout these papers was a difference between the usage of e-cigarettes compared to traditional cigarettes. In one study, researchers found that the participants significantly increase the average time they puffed on e-cigarettes (Ceriana et al., 2015). Another study also showed that although e-cigarettes deliver less nicotine to their users, the devices were smoked more intensely than traditional cigarettes (Norton et al., 2014). After finishing, these participants were also less satisfied.

Table 2: Ideas in Literature about Electronic and Traditional Cigarettes

	Short Term Evaluation of Health E-ffects (< 1hr)	**E-cigarettes induced adverse effects**	**Difference between the usage of e-cigarettes and traditional Cigarettes**
(Pepper et al., 2014)			
(Ferrari et al., 2015)	*X*		
(Vargas Trassierra et al., 2014)	*X*	*X*	*X*
(Papoušek et al., 2014)	*X*		*X*
(Lee et al., 2015)		*X*	*X*
(Harrington et al., 2015).		*X*	*X*

(Farsalinos et al., 2017)		*X*	*X*
(Norton et al. , 2014)	*X*	*X*	*X*

Generations of E-Cigarettes

The papers within this section have two major ideas. E-cigarette users have preference over the design of the e-cigarettes. E-cigarettes also have a difference in the delivery of nicotine, which is dependent on the design. Research conducted in one of the papers found that third generation e-cigarette users consume twice the amount of e-liquid compared to second generation e-cigarette devices (Dawkins et al., 2014).

Table 3: Ideas in Literature in relation to Generation of E-cigarettes

	Differences in the delivery of Nicotine	**Short term Evaluation of Health Effects**	**User preference differs with design**	**Promotion of Smoking Cessation**
(Rüther, et al., 2017)	*X*	*X*	*X*	*X*
(Dawkins et al., 2014)	*X*	*X*	*X*	*X*
(Chen, Zhuang, & Zhu, 2016)	*X*			*X*
(Lechner et al., 2015)	*X*		*X*	
(Wagener et al., 2016)	*X*		*X*	
(Farsalinos et al., 2015).	*X*	*X*	*X*	

E-liquids and Aerosols

The research in this category differed by the variables researchers chose to measure. Some looked at the particles in the aerosol, while others looked at the chemicals in the user's body. Two major findings within this section were that e-liquids alter the behavior of the smoker and that the design of the device impacts the aerosols. For the first finding, seven papers

illustrated how the behavior of the smoker was altered by the e-liquid. For example, in one study, higher levels of carbonyls were related to intensive puffing. This demonstrated that individuals using e-liquids of lower nicotine concentration puff longer to increase their exposure of these nicotine (Corcoran et al., 2017). The second finding illustrated how design of the e-cigarettes impacts the aerosol of e-cigarettes. In a study, researchers found higher concentrations of metals in the e-liquid within different areas of the e-cigarette devices (Olmedo et al., 2018). The tank and the aerosol had the highest level of metal concentrations, indicating that e-liquid contamination is occurring throughout the process of using e-cigarettes.

Table 4: Ideas in Literature about E-liquids and Aerosols

	E-liquids can alter the behavior of the smoker	**The level of substances (metal, compounds, and chemicals) in a smoker's system increases**	**Negative health effects due to the e-liquid**	**Design of e-cigarettes can impact the aerosol of the e-cigarettes**
(Corcoran et al., 2017)	*X*			
(Pourchez et al., 2018)	*X*	*X*		
(St. Helen, 2018)			*X*	
(Strongin, 2019)	*X*			*X*
(Kaur et al., 2018)	*X*			*X*
(Erythropel et al., 2018)	*X*			*X*
(Korzun et al., 2018)		*X*	*X*	
(Klager et al. 2017)				*X*
(Dawkins et al., 2016)		*X*		*X*
(Dawkins & Corcoran, 2013)	*X*			
(Papoušek, 2014)				*X*
(St. Helen, 2017)	*X*			
(Olmedo et al., 2018)		*X*		*X*

Overall

The papers gathered for this literature review provide insight into how the different components of e-cigarettes affect their usage. Compared to traditional cigarettes, e-cigarettes are used differently, which can be illustrated through the differences in the smoking behavior of the users. Also, the creation of e-cigarettes, initially, was to provide aid in smoking cessation, however, there are contradictions in the findings provided by the literature. When comparing traditional cigarettes to e-cigarettes, Harrington et al. (2015) found that while e-cigarettes decrease the frequency of smoking, they are not effective in promoting smoking cessation. This finding differs from the research of Chen et al. (2016) where they found that second generation devices promote both smoking cessation and satisfaction.

E-cigarettes also differ from traditional cigarettes due to their ingredients. Although there are lower concentrations of harmful ingredients within e-cigarettes, it should not discount the fact that they are still harmful. Allen et al. (2017) found that all of the e-cigarettes contained chemicals that were considered dangerous by the FDA or Federal Emergency Management Agency (FEMA). Most of the research conducted illustrate that traditional cigarettes have higher toxic ingredients; however, this should not be the only benchmark to assess the healthiness of e-cigarettes. The comparison only shows that e-cigarettes are better than traditional cigarettes, not that they are harmless. Also, other considerations have to be made when assessing the harm of e-cigarettes. There is an abundance of chemical reactions undergone throughout the vaping process. For example, Erythopel et al. (2018) found that the conversion of aldehydes, a highly reactive functional group, to acetals initiate the activation of irritant receptors within cells. Therefore, the contents of the aerosols become an important indicator of exposure to harmful materials.

Most of the papers, regardless of the subject area, focused on the topography, or smoking behavior of the users. Research by Dawkins et al. (2017) and Lee, Gawron, and Goniewicz (2015) have different objectives, however, they were both conducted similarly utilizing patient studies to collect user data. From the data, they were able to compile measurements regarding the number of puffs, the duration of the puff, and the satisfaction of the user. Another common finding between the research is the measurement of nicotine levels, which could be collected from either the blood stream or aerosol of the users. Corcoran et al. (2016) measure nicotine levels within the bloodstream while Farsalinos et al. (2017) measure nicotine levels within aerosols. The final idea prevalent in the research is the ingredients within these e-cigarettes, which can be examined through the e-liquids or the aerosols created by the device. From this information, several areas appear significant when evaluating e-cigarettes: Smoking Topography & Behavior, Assessment of Nicotine, and Aerosol Toxicity.

CHAPTER 5B: CONTENTS OF PMTA

The Premarket Tobacco Product Application (PMTA) is broken into five distinct sections: Executive Summary, Review of the PMTA, Product Labeling, Consumer Comprehension, & Marketing Plan, and Conclusions & Recommendations. Specifically, Review of the PMTA contains multiple subsections selected by the Center for Tobacco Products as areas necessary for the evaluation of the electronic cigarette device created by the Phillip Morris S.A. These research areas include but are not limited to behavior clinical pharmacology, chemistry, environmental science, epidemiology, and toxicology. This section is used to examine the research Phillip Morris included in the PMTA. Particularly, experiments categorized under that areas from literature review that were deemed important.

Smoking Topography

Smoking topography describes the behavioral patterns of a smoker. It encompasses elements such as the number and length of individual puffs a person takes while smoking (Robinson et al., 2018). Through behavioral analyses, topography can illustrate the difference in smoking regimens between different types of smokers and even the selection of settings on a smoking machine used by researchers to replicate human smoking behavior.

Within the PMTA, Phillip Morris S.A. conducted four studies looking at the behavior of individuals in the United States(1), Europe(1), and Japan(2). Within the United States, the study observed 160 participants over a 91-day period, including 5 days within a confined setting and 86 days within an ambulatory setting. Participants consisted of healthy individuals who were at least 22 years and older and smoked at least 10 menthol cigarettes per day (Lewis and Farmer 2016). There were three different groups within the study:

- Experimental group: Individuals who used the THS 2.2 Menthol device ad libitum for 5 days in the confined environment and 86 days in an ambulatory environment
- Active comparator group: Individuals who used their own preferred brand of traditional menthol cigarettes ad libitum for 5 days in the confined environment and for 86 days in their ambulatory environment.
- Sham Comparator group: Individuals who abstained from smoking for 5 days in a confinement environment and 86 days in an ambulatory environment

For evaluation of the Phillip Morris S.A product, participants were given a self-report questionnaire called the Modified Cigarette Evaluation Questionnaire. From this survey, researchers were able to compare the craving reduction, enjoyment of respiratory tract sensation, and smoking satisfaction between the experimental group and the active comparator group. Researchers found that every category was lower for the experimental group, the individuals using the Phillip Morris S.A. device. Table 5 illustrates the statistical analysis of the results collected from the survey (Farmer and Lewis, 2016).

The researchers noted that over time these variations between the groups decreased, so there were no notable differences. However, these decreases in magnitude over time can be explained not only by the differences in smoking topography between the smokers, but also due to the active comparator group using their preferred cigarettes, resulting in stability of their data. Upon closer examination, although craving reduction was lower, the category was still higher in magnitude compared to any of the other categories. If cravings are not reduced by the device, then it introduces the questions of whether individuals are actually satisfied and whether they would smoke more due to the lack of reduction in their urge to smoke.

Table 5: Results from the Modified Cigarette Evaluation Questionnaire during the 91-day US study comparing users smoking traditional menthol cigarettes or the Phillip Morris S.A. device, THS 2.2 Menthol (Lewis and Farmer, 2016).

Difference Between THS 2.2 Menthol and mCC Scores for MCEQ Subscales – PP Set		
	Difference THS 2.2 Menthol - mCC	
MCEQ Subscale/Time point	Difference	95% CI
Aversion		
Day 1	-0.10	-0.47, 0.28
Day 5	0.15	-0.20, 0.49
Day 90	0.08	-0.18, 0.34
Craving reduction		
Day 1	-1.6	-2.3, -0.9
Day 5	-1.1	-1.8, -0.4
Day 90	-0.7	-1.4, 0.0
Enjoyment of respiratory tract sensation		
Day 1	-1.1	-1.7, -0.4
Day 5	-0.6	-1.3, 0.1
Day 90	-0.2	-0.8, 0.5
Psychological reward		
Day 1	-0.91	-1.38, -0.45
Day 5	-0.40	-0.86, 0.06
Day 90	-0.30	-0.78, 0.17
Smoking satisfaction		
Day 1	-1.46	-2.03, -0.89
Day 5	-0.96	-1.50, -0.42
Day 90	-0.37	-0.88, 0.13
Abbreviations: mCC = Menthol conventional cigarette; CI = confidence interval; MCEQ = Modified Cigarette Evaluation Questionnaire; PP = per protocol; THS 2.2 Menthol = Tobacco Heating System 2.2 Menthol.		

Within the clinical study, smoking topography was characterized by examining puff volume, puff duration, flow, and puff frequency. During the ambulatory phase, researchers observed differences in average flow, total number of puffs, puff frequency, and total smoking time between the two groups. Although users of the THS 2.2 Menthol device had a shorter smoking time, they had higher total numbers of puff, puff frequency, and average flow. The value of these differences can be found below in Table 6.

Table 6: Smoking Topography comparisons in the ambulatory phase of the study (86 days) comparing smokers using traditional cigarettes of the Phillip Morris S.A device.

Category	Difference	Larger for Individuals using the THS 2.2. Menthol Device
Average Flow (mL/s)	7.41	x
Number of Puffs	3.34	x
Smoking Duration (min)	1.5	
Puff Frequency (puff/min)	2.22	x

Pharmacological Assessment of Nicotine

Pharmacology describes the interactions of drugs within the body. It is commonly broken in to two areas of study: pharmacodynamics (PD) and pharmacokinetics (PK). Pharmacodynamics surrounds the response of the body due to the drug, while pharmacokinetics surrounds the movement of the drug itself ("Pharmacokinetic & Pharmacodynamic Services: Nuventra.", n.d.). Nicotine is commonly found in tobacco products, including the THS 2.2 Menthol device. Within the PMTA, Phillip Morris S.A. included data collected from a study used to research the PK and PD of nicotine from three different products, the heatstick of the THS 2.2 Menthol device, traditional menthol cigarettes, and nicotine nasal spray (NNS). The 6-day study was comprised of healthy individuals between 22 and 65 years old who smoked for at least 3 consecutive years and smoked at least 10 traditional menthol cigarettes per day (Borders, n.d.). The study was broken into two periods which each consisted of one day (at least 24 hours) of nicotine abstinence and 1 day using one of the products. During the study, the participants interacted with two of the three nicotine products. There were four groups, which differed by the

sequence of interaction the participants had with the products during the periods. They are as follows:

- Group 1: single heatstick of the THS 2.2 Menthol (period 1) | ad libitum use of traditional menthol cigarette (period 2)
- Group 2: ad libitum use of the traditional menthol cigarette (period 1) | single heatsick of the Nasal nicotine Spray (period 2)
- Group 3: single heatstick of the THS 2.2 Menthol (period 1) | single heatstick of the one spray per nostril of the Nasal Nicotine Spray (period 2)
- Group 4: one spray per nostril of the Nasal Nicotine Spray (period 1) | THS 2.2 Menthol (period 2)

Within the experiment, there were two pharmacokinetic comparisons, one between the THS 2.2 Menthol device & traditional menthol cigarette and another between the nasal nicotine spray & THS 2.2 Menthol device. The pharmacokinetic comparisons illustrate the relationship between the concentration of nicotine in the bloodstream (plasma) over time, ranging from 0 to 24 hours. Between the traditional cigarette and the heatstick, the shapes of the PK nicotine concentration-time curves were similar however, there were lower concentrations of nicotine for smokers using the heatstick compared to the nicotine cigarettes. Another difference was the time necessary to reach the maximum nicotine concentration, which was shorter for the heatstick. The exposure of nicotine, denoted by the area under the nicotine pharmacokinetic curve to the last quantifiable concentration ($AUC_{0\text{-last}}$), was lower for the heat stick compared to the traditional menthol cigarette, 16.5 ng*h/mL and 29.7ng*h/mL, respectively. After completion of the statistical analyses for both products, researchers noticed large amounts of between-subject

variability, which indicates that the relationship of the nicotine within the plasma differed between individuals in the study.

Conversely, the next comparison, between the heatstick and the nicotine nasal spray, showed different results. Specifically, the exposure to nicotine, denoted by $AUC_{0\text{-last}}$, was significantly higher for e-cigarettes. The values were 15.6 ng*h/mL and 8.7 ng*h/mL, respectively. However, researchers still noticed very large values for the between-subject variability for all of the pharmacokinetic parameters that were analyzed.

Due to its longevity within the body, cotinine, a metabolite of the nicotine, is commonly used as another method to analyze nicotine exposure (CDC, n.d.b). Another portion of the study focused on the plasma cotinine levels, beginning after at least 24 hours of smoking abstinence and before using the nicotine product, which is indicated by T_o. There were three time points used in the analysis: T_o, T_o+12hr, and T_o+24hr. Between the two cigarettes, the traditional and the electronic cigarettes, the concentration of cotinine were similar between 12 hours, however, after the 24 hours the concentration decreased further than baseline. This ultimately was not was not significant. The values are indicated below in Table 7.

Table 7: Average plasma cotinine concentrations used to evaluate nicotine exposure within individuals who smoked using either the THS 2.2 Menthol device or the traditional menthol cigarettes

	THS 2.2 Menthol device (ng/mL)	**Traditional menthol cigarette (ng/mL)**
T_o	38.0	29.4
T_o + 12 hr	29.8	33.5
T_o + 24 hr	20.8	25.7

The study also looked at the differences between the plasma cotinine concentrations for individuals using the NNS and the THS 2.2 Menthol device. The same time points were used as in the previous comparison between the THS 2.2 Menthol device and the traditional menthol cigarette. As shown in Table 8, there is decline within both of these products over time. There are differences between the values of the nicotine nasal spray and the Phillip Morris S.A. device, however, researchers classified these differences as insignificant.

Table 8: Average plasma cotinine concentrations used to evaluate nicotine exposure within individuals who smoked using either the THS 2.2 Menthol device or the nicotine nasal spray

	THS 2.2 Menthol device (ng/mL)	**NNS (ng/mL)**
T_o	28.2	27.3
T_o + 12 hr	24.3	21.2
T_o + 24 hr	17.1	14.2

Aerosol Toxicity

When looking at the toxic effects of the THS 2.2 Menthol device, Phillip Morris S.A. submitted data from both in vitro and in vivo clinical studies. Within the research, Phillip Morris S.A. focused on the comparison between the aerosols of the heat stick from THS 2.2 Menthol device and the smoke created from the 3R4F, a standard reference traditional cigarette created by the University of Kentucky College of Agriculture ("3R4F", n.d.).

Before those studies, an initial test was completed to determine the different chemicals within the aerosols and smoke of the respective products. The screening of the two tobacco products indicated that there were 80 chemicals in the heatstick aerosol that were in higher

concentration or non-existent compared to the smoke from the 3R4F reference cigarettes. Most of these chemicals were either considered Generally recognized as Safe (GRAS) by the FDA (30 chemicals) or used as ingredients to flavor the product (46 chemicals). Although the remaining ingredients were considered carcinogenic, Phillip Morris S.A, indicated that they didn't pose a concern due to their low concentrations, which were below the permissible exposure limits (PELs) set by Occupation Safety and Health Administration (OSHA). The Center for Tobacco Products (CTP) did not agree with Phillip Morris S.A.'s interpretation of OSHA standards because they had no relationship in regard to how the THS 2.2 Menthol device would be used (FDA, 2019, p. 32). The PELs scope is limited to the workplace, which is not the only environment where the use of the Phillip Morris S.A. device would be used (FDA, 2019, p. 32).

By using the Organisation for Economic Co-operation and Development's (OECD's) Quantitative Structure-Activity Relationship, Phillip Morris S.A. was able to conduct further research into toxicity of these chemicals (FDA, 2019, p.32). The technique utilizes the molecular structures of the chemicals to estimate the potential dangers associated with their chemical properties. Ultimately, 19 of those original 80 chemicals, most of them being the flavoring ingredients, were found to be potentially genotoxic or carcinogenic.

Two in vitro tests used in the application were the Neutral Red Uptake (NRU) assay and Bacterial Reverse Mutation test. The aerosol and smoke of the products can be broken into two different groups: total particulate matter (TPM) and gas vapor phase (GVP). TPM consists of particles that can be trapped by a glass-fiber pad, while GVP refers to the particles that pass through the same pad. The Neutral Red Assay was used to detect viable cells after 24-hr exposure to culture medium containing the TPM or GPV fractions of the THS aerosol or the 3R4F smoke. This experiment resulted in needing higher concentrations of the aerosol TPM and

GVP compared to the smoke of the 3R4F in order to reach an effective concentration that reduces the cell population by half (EC_{50}), which indicates that the aerosol was less toxic. The Bacterial Reverse Mutation Test was used to find chemicals within the TPM fractions of the aerosol or the smoke causing bacteria to mutate ("Pre-Clinical Assessment Summary", p. 3). The experiment found that unlike the reference cigarette, the fractions of the aerosol did not produce a mutagenic response within the bacteria.

In vivo studies included a 3-month nose-only inhalation rat study and an 18-month carcinogenicity mouse study. In the first study, the rats were exposed to the smoke, aerosol, or filtered air, which was used as a control. There was a vast number of biological endpoints that were examined throughout the study. Overall, most of the endpoints were lower in the aerosol compared to the smoke. However, interestingly, the prevalence of cell hyperplasia, cell proliferation that leads to the enlargement of organs (commonly leading to cancer), were similar in the inhalations of aerosol and smoke. In the 18-month study, the same process was used but in mice. This was used to identify the risk of cancer. The conclusions from this study indicated that the was no increase risk to lung cancer for mice exposure to the THS 2.2 aerosol compared to the control group.

Summary

The research submitted in the PMTA provides evidence for three subject areas that are important in analyzing the risks of e-cigarettes: Smoking Topography, Assessment of Nicotine, and Aerosol Toxicity. In regard to smoking topography, the research included in the PMTA reveals that smoking behavior is different between the two products. Specifically, individuals using THS 2.2 Menthol device had a higher amount of puff, higher puff frequency, and higher

average flow rate. From the assessment of nicotine, the research focused on the pharmacodynamics of nicotine. Comparing the curves of the THS 2.2 Menthol device and the traditional cigarette, the assessment of nicotine showed that although they both contain nicotine, individuals using the THS 2.2 Menthol device were exposed to less nicotine. Finally, when assessing the toxicity of the aerosols from the THS 2.2 Menthol device, the results emphasize the toxicity of the aerosol. However, when the data is compared to that of the reference cigarette, 3R4F, the results show that the THS 2.2 Menthol toxicities are lower than those created by the traditional cigarette.

CHAPTER 5C: COMPARISON BETWEEN THE FINDINGS

From the PMTA, we can see that Phillip Morris S.A. included research from areas identified by the literature review as being important. Since these areas were covered, the next step to analyze the regulatory process is to compare the findings from the PMTA to the findings from the research gathered in the literature review. By comparing the finding, we can show whether the research within the PMTA was consistent with the ideas of the literature.

Smoking Topography

Although this PMTA evaluates multiple pieces of evidence submitted by Phillip Morris S.A. to validate the THS 2.2 Menthol device, the conclusions obtained are based on the comparisons between traditional cigarettes and e-cigarettes. These two devices provide a solution for the same need; however, the technology of their designs is vastly different. Literature can be used to provide examples supporting or opposing the claims founded from the data of the experiments used within the PMTA.

From the literature review, research shows that there is dissimilarity in topography not only amongst the variation of e-cigarettes but also between traditional and electronic cigarettes. Like the research from the literature review, the findings of the PMTA also verify that smokers use traditional cigarettes and e-cigarettes differently. If these devices are used differently, should they still undergo the same evaluation process? There are many different behavioral aspects that play a role in analyzing the topography of smokers. Overall, the PMTA concluded that the smoking topography was different, however, Table 5 provides a closer look into specific variables within smoking topography. It will be used to illustrate whether the claims are supported by both the findings from the PMTA and the findings from the literature review.

Table 5: Variables that can be affected by smoking topography indicated by the findings within literature.

Findings from Literature Review	**Agree with PTMA findings**	**Implications for Consumer Safety/ Health**
E-cigarettes modify smoking behavior through having smaller and longer puffs. (Lee et al., 2015)	NO. The findings show that puff volume and puff duration were similar.	HIGH
Significant differences were indicated for puff volume due to the flavor of the e-cigarette. (Robinson et al., 2018)	NO. There were no significant differences in puff volume. The PMTA focused on traditional and e-cigarettes, while the research focused only on e-cigarettes.	HIGH
Nicotine levels change when puff durations are longer. (Farsalinos et al., 2017)	Did not test.	HIGH
Lower nicotine e-liquids were associated with higher puffing topography (Dawkins et al., 2016), which can increase exposure to Harmful and Potentially Harmful Constituents (Robinson & Hensel, 2019).	Did not test. There was no variation between the amount of nicotine in the heatsticks used in the study.	HIGH
ENDS were significantly higher in total volume and inter-puff interval. (Norton et al. , 2014)	YES. The was a difference between total volume between the two products. The THS 2.2 Menthol remained higher throughout the study.	HIGH
Significant differences were indicated for puff flow rate due to the flavor of the e-cigarette. (Robinson et al., 2018)	YES. There was a difference between the puff flow rate but for the comparison of traditional and e-cigarettes.	MEDIUM

Topography changes can alter many of the processes that occur while smoking. For example, it can affect the chemicals and particles that are introduced to the user (Robinson and Hensel, 2019 & Farsalinos et al., 2017). Due to the hazard surrounding some of the chemicals, the health of the users can be altered due to how they are using the device. Although the parameters of the experiments within the PMTA do not focus on this relationship, topography can also be influenced by the strength of the nicotine that is used in the formula of e-liquids, or in this case the heatstick. Robinson and Hensel (2019) as well as Corocan (2016) found similar evidence that suggests that the concentration of nicotine can alter the behavior of the smoker. The support between literature and research completed within PMTA confirm that there are differences in the topography between smokers. There is, however, dissimilarity between the implications that this can have in regard to both the system and the user.

Pharmacological Assessment of Nicotine

Due to is addictive properties and reactions inside the body, the exposure of nicotine is really important, especially when considering the dangers of tobacco from a health perspective. Within the PMTA, the study focused on the pharmacokinetic factors associated with nicotine. Table 6 illustrates research that focuses on how nicotine is affected when comparing different tobacco products. As previously mentioned, the literature shows that there is a difference between smoking topography between traditional cigarettes and e-cigarettes. However, due to the differences between findings, the review of literature was inconclusive in determining whether electronic cigarettes are capable of promoting smoking cessation. Within the PMTA, the research indicated there was higher nicotine exposure in traditional cigarettes compared to e-cigarettes. Just because there is less exposure of nicotine compared to the traditional cigarettes,

does this mean the device safe? It indicates that there is less harm, but does less harm equate to more safety of the user?

Table 6: Observation of the effects of smoking on nicotine within the literature.

Findings from Literature Review	**Agree with PTMA findings**	**Implications for Consumer Safety/ Health**
Levels of nicotine increased faster in the traditional cigarette compared to the cigalike and the tank model e-cigarettes (Rüther et al., 2018).	NO. The THS 2.2 Menthol device reached its maximum nicotine concentration faster than the traditional cigarette	HIGH
The exposure to nicotine is impacted by the preference of the flavor. (Dempsey et al., 2017)	NO. The PMTA found that they were comparable for both the fresh and menthol flavored heatsticks.	HIGH
Concentration of nicotine in the blood plasma increased significantly. (Dawkins & Corcoran, 2013)	NO. Compared to the concentration of traditional cigarettes, the nicotine levels from the THS 2.2 Menthol did not increase significantly.	HIGH
The nicotine plasma concentrations were higher in traditional cigarettes. (Rüther et al., 2018)	YES. The plasma concentrations were higher in traditional cigarettes.	HIGH
Urge to smoke decreased, but after the end of the smoking period is was not significant. (Dawkins & Corcoran, 2013)	NO. Craving reduction reduced, but it was still less than traditional cigarettes.	HIGH

One thing that was not observed within the literature review was the comparison of e-cigarettes to nicotine replacement therapy (NRT). Nicotine nasal spray (NNS) is used to help

individuals quit smoking by lowering the symptoms associated with withdrawal. This area of the study indicated significant differences between the nicotine exposure of both the NNS and the e-cigarette. Although the research within the PMTA shows the urge to smoke was less when using the NNS compared to the e-cigarette, the THS 2.2 Menthol system has the ability to expose users to both higher amounts of nicotine as well as a higher number of Harmful and potentially harmful constituents (HPHCs). This indicates that if smokers stop using traditional cigarettes, they would begin using a device that still can expose them to hazardous chemicals. One study within the PMTA focused on the likelihood of cigarette smokers in switching to electronic cigarettes (THS 2.2 Menthol). During a 6-week period, around thirty-four percent of individuals initially began using the e-cigarette, however, within that group only sixteen percent were solely using the THS 2.2 Menthol device by week 6, and sixteen percent of individual reverted to using traditional cigarettes prior to week 6.

Similar to the research within the PMTA, Hagedorn et al. (2013) found that the plasma nicotine levels are higher in traditional cigarettes, however, the findings between these two conflicts when looking at the time it takes to reach the maximum nicotine plasma concentration. The research in the PMTA shows a shorter time for individuals using the THS 2.2 Menthol, while the Hagedorn et al. (2013) indicates the traditional cigarettes were shorter. Differences in time it takes to reach the maxima could not only have implications in understanding more about user satisfaction as well as why smokers continue to smoke.

Aerosol Toxicity

Although there is less exposure to nicotine in electronic cigarettes, it does not discount the other harmful chemicals that are within both types of cigarettes. Within the PMTA, there is

an abundance of studies that focus on the toxicity of aerosols. Before these compounds and chemicals can be tested for toxicity, they first have to be identified. Using different methods to capture particulates from the TPM or the GVP can lead to different results (Eddingsaas et al., 2018). Within their study, Eddingsaas et al. (2018) found that particles differ depending on the substance that you are testing, either the aerosol or the e-liquid. They also found differ by the method you are collecting them, for example, filter pads or methanol impingers have different efficiencies during collection. The variations between methods and results confirm the need for a standardized method of identifying chemicals in e-cigarette. The individuals from the Center for Tobacco Products also suggested their uncertainty about how Phillip Morris S.A.'s collection method could possibly impact the study.

From the research within Table 7, there are a number of considerations that need to be made when evaluating electronic cigarettes. During their research, Olmedo et al., (2018) found that metals can be transferred through the smoking process using e-cigarettes. Although there was data in the PMTA examining the engineering aspect of the THS 2.2 system, there were no tests investigating the potential cross-contamination between the metal of the device and product. Most of the comparisons within the PMTA focused on comparing traditional cigarettes to the electronic cigarettes, however, due to the differences in technology there are more areas that should receive testing.

Table 7: Differences in aerosols findings between research in the literature.

Findings from Literature	Agree with PTMA findings	Implications for Consumer Safety/ Health
There are a variety of chemical reactions that occur through the process of using an e-cigarette. (Strongin, 2019)	YES. The PMTA tested the ingredients within the heatstick aerosol.	HIGH
E-cigarettes have a higher number of radon decay products, which led to an increase in the particle number concentration. (Vargas Trassiera et al., 2014)	Did not test. The PMTA only tests the toxicity of the ingredients found in the aerosol.	LOW
The use E-cigarettes enable metals to be transferred, exposing the users to toxic materials. Found that metal concentrations were higher in the aerosol than the tank. (Olmedo et al., 2018)	Did not test. The PMTA does not disclose the particles within the TPM just the comparison between the two products.	HIGH
Some methods provide different levels of accuracy in capturing the compounds with the aerosol and the e-liquids. (Eddingsaas et al., 2018)	Did not test. The only thing altered were the smoking regimens of the smoking machines. PMTA did not disclose what they used to capture the TPM or the aerosols.	HIGH
Cell-specific responses were dependent on the chemical introduced to the cells. Some responses were more potent than others. (Gerloff et al., 2017)	Did not test. The in vitro studies indicated toxicity but did not show how function was altered.	HIGH

CHAPTER 5D: QUALITY OF DATA

The studies previously mentioned allow the Center for Tobacco Products to conclude that these devices are safe for the public. Although most of the evidence support these claims, there are a number of concerns within the studies that could potentially impact the decision to approve the device.

This smoking topography study was done in order to determine differences; thus, these differences could illustrate how smokers really interact with the THS 2.2 Menthol device which are different from traditional cigarettes. Researchers claimed that these disparities were caused by the "process of adaptation" for participants using the THS 2.2 Menthol. These devices are different, so the method or technique of smoking would be modified. However, in order to counteract these adjustment effects regarding the device properly in the study, researchers could have either conducted a longer study, provided a more extensive tutorial about the THS 2.2 menthol devices, or given a longer period in the controlled environment to assess whether participants were using the new device properly.

The design of the pharmacology study of nicotine could have been altered to create a more compelling argument. The behavioral data collected from the smoking topography study indicates that there is a difference between the smoking behavior when using the different tobacco products. As a result, smoking preference could influence the amount of nicotine introduced in the system of the smokers due to their smoking behavior. Also, the MCEQ in the behavioral study shows that over the 90 days smokers start altering their opinions of the device. This introduces whether 5 days is enough for smokers to develop a consist smoking behavior that reflects how individuals using the new THS 2.2 Menthol device would use the product.

Overall, the CTP found that it was difficult to assess the long-term exposure using the data provided from the in vitro and in vivo studies. For example, most data within the in vitro studies confirmed that the THS 2.2 Menthol device needed higher concentrations to create the similar toxic effects as the 3R4F. However, the CTP noted that there is no validation behind the method of generating the aerosols of the heatsticks. For the in vitro studies, the CTP also indicated concerns about accepting whether the studies provide enough evidence to accurately predict the carcinogenic potential of aerosol exposure.

Overall

Although most of the categories associated with high health implications were covered in the PMTA, majority of its findings were not consistent with the research from the literature review. This section, however, emphasizes the findings that were not covered in the PMTA, which are also are illustrated in Table 8. Although some of the experiments in Table 8 are not applicable with research within the PMTA, they are still included because of their implications regarding consumer safety. For example, Corocan (2016) as well as Robinson & Hensel (2019) showed that the strength of nicotine impacts smoking behavior. Although the THS 2.2 Menthol doesn't use e-liquids, an experiment still could have looked at the how the strength of the Heatsticks impacts user behavior. One area that was overlooked within the PMTA was the studies that show the interaction of all the device components. The research conducted by Olmedo et al. (2018) reveal that users can be exposed to metal components that are inside the device. This has a huge impact in consumer safety due to the design of e-cigarettes, which use different metals. Due to their significance, these areas should be incorporated into the PMTA process so that the entirety of the device is accurately analyzed.

Table 8: Findings from the literature review that were not covered within the PMTA

Findings from Literature Review	Agree with PTMA findings	Implications for Consumer Safety/ Health
Nicotine levels change when puff durations are longer. (Farsalinos et al., 2017)	Did not test.	HIGH
Lower nicotine e-liquids were associated with higher puffing topography (Dawkins et al., 2016), which can increase exposure to Harmful and Potentially Harmful Constituents (Robinson & Hensel, 2019).	Did not test. There was no variation between the amount of nicotine in the heatsticks used in the study.	HIGH
E-cigarettes have a higher number of radon decay products, which led to an increase in the particle number concentration. (Vargas Trassierra et al., 2014)	Did not test. The PMTA only tests the toxicity of the ingredients found in the aerosol.	LOW
The use E-cigarettes enable metals to be transferred, exposing the users to toxic materials. Found that metal concentrations were higher in the aerosol than the tank. (Olmedo et al., 2018)	Did not test. The PMTA does not disclose the particles within the TPM just the comparison between the two products.	HIGH
Some methods provide different levels of accuracy in capturing the compounds with the aerosol and the e-liquids. (Eddingsaas et al., 2018)	Did not test. The only thing altered were the smoking regimens of the smoking machines. PMTA did not disclose what they used to capture the TPM or the aerosols.	HIGH
Cell-specific responses were dependent on the chemical introduced to the cells. Some responses were more potent than others. (Gerloff et al., 2017)	Did not test. The in vitro studies indicated toxicity but did not show how function was altered.	HIGH

CHAPTER 6: DISCUSSION & CONCLUSION

Within this chapter, I will discuss the implications of the PMTA analysis, summarize the limitations of research, and provide recommendations for the current evaluation process of e-cigarettes.

CHAPTER 6A: IMPLICATIONS OF THE PMTA

The main comparison being made throughout the entirety of the PMTA is between traditional cigarettes and e-cigarettes. All of the research conducted include the use of traditional cigarettes to show the differences in the levels of harm between the two products. Throughout most of the PMTA, the evidence provided depicts the image that electronic cigarettes are less harmful than traditional cigarettes; however, less harmful does not equate to harmless. These devices are "less harmful" compared to traditional cigarettes, which have been known to have detrimental effects. This means that the device is still harmful. If the foundation of this analysis was based solely on e-cigarettes, rather than a comparison, would the decision of the CTP to approve this device be the same?

The first research question of this thesis surrounds whether the evidence provided by companies was substantial. This question was used to examine not only the information that companies provided, but also the strength of the evidence used to justify the safety of the electronic cigarette device. The PMTA completed by Phillip Morris incorporated different areas of research, however under closer observation, the work done does not provide strong enough arguments to be considered substantial.

Some of the experiments that were selected to build arguments for the safety of the THS 2.2 Menthol device, in particular, were either not verified or did not show conclusive results. As

previously shown, the Center for Tobacco Products had concerns regarding the in vitro tests, which were used to show the carcinogenic potential of the aerosol. They also were unsure whether using the particulate matter or the gas vapor phase impacted the results of the experiments that were being done. These questions regarding the quality of the experiments ultimately reduce the efficiency of the regulation process. If companies are able to submit evidence that doesn't solidify a strong argument of safety, then the decision by the Center for Tobacco Products to mark these devices as safe doesn't rely solely on the science.

One main focus of this regulation is to accurately assess the safety of these devices. If there are holes in the argument, like the inconclusiveness of results, then how can the FDA support the idea that these devices are safe. Within the process of regulating these devices, the FDA can request more information from the companies. However, it seemed as though these instances of concern or evidence of ambiguity did not warrant the FDA to pursue this route.

From the PMTA, we see Phillip Morris includes multiple studies to justify the safety of the THS 2.2 Menthol device. Although there is an abundance of evidence provided, there are still questions surrounding the quality of the experiments they chose to include. The FDA has the final decision in approving these devices, but they have to determine whether the evidence provided is satisfactory in showing safety. Despite approving these devices, the FDA was not able to accurately assess the THS 2.2 Menthol device due to the limitations of the research that was provided.

The second research question addresses whether the regulation process is effective for analyzing e-cigarette devices. Despite the inclusion of important research areas in the PMTA, more research needs to be done in order to effectively analyze e-cigarette devices. The emphasis of traditional cigarettes within the PMTA eliminated the need for research that placed attention

on simply e-cigarettes. For example, the in vitro studies focused only on the toxicity of the aerosols in relation to genetics, however, there was no research that indicated whether the use of this device generates functional changes in the cells. The lungs are an important part of respiratory system, particularly for its blood-air interface, which regulate gas exchange within the body. The barrier associated with the cells of the lungs have the ability to filter particles, restricting them from entering the bloodstream. Since the route of transmission affects the respiratory system, research that shows how the aerosols affect cellular structures should be important in the assessment of the e-cigarettes.

Also, the representation of potential users was limited within all of the clinical studies. Phillip Morris S.A. claimed that the THS 2.2 Menthol device was only aimed at current and former smokers, but the studies focused solely on current smokers. Groups of individuals, like former smokers, non-smokers and youth, were not included. Phillip Morris S.A. used data from a likelihood of use study to verify the potential types of users that would interact with their product. From the study, Phillip Morris S.A. concluded that these groups were not going to be using their products. However, McKenley et al. (2018) found that Phillip Morris's data was unsuccessful in confirming that youth, specifically, would neither find their products alluring nor start using them [20]. From the current increase use of e-cigarettes by the youth, the results from Phillip Morris seem likelihood of use study seem unlikely.

Within their application, Phillip Morris S.A indicated that the FDA did not expect youth representation within the studies. However, like most of their research in the PMTA, which focused on the comparison between cigarette products, Phillip Morris S.A. could have included information about the youth interactions with any of their other products for a comparison but did not (p.76). By limiting the research to individuals who are current smokers, we are unaware

of the effects that could happen for individuals who do not smoke but would consider using e-cigarettes.

Finally, many of the conclusions from the studies included within the PMTA were not supported by the research from the literature, which had high implication for the health of the consumer. Some elements were not even examined within the PMTA. There are a multitude of differences between traditional cigarettes and e-cigarettes, especially when considering technology. The system of Phillip Morris is more complex than a traditional cigarette, yet no research looked at whether the heating elements of the system interacted with the user. Since they were not addressed, it is difficult to say that this process is effective because not all of the health implications are considered when analyzing e-cigarettes.

The effectiveness of the regulation process for e-cigarettes is limited by the process that is currently in place to evaluate its predecessor, the traditional cigarette. To be effective, the process for regulating e-cigarettes cannot rely solely on the research that is required for traditional cigarettes. The research needs to include information that focuses on the technological differences that makes these devices, e-cigarettes, more complex than traditional cigarettes. The regulation process was effective due the inclusion of important research areas required in analyzing these devices, however, in order to make an accurate evaluation of these e-cigarette devices, more focus needs to be placed on the e-cigarettes rather than the comparison between the traditional cigarettes and electronic cigarettes.

CHAPTER 6C: LIMITATIONS OF RESEARCH

The biggest limitation of the research conducted in this thesis is the access to PMTAs. There was only one application for e-cigarettes available on the FDA website. In order to effectively assess the evaluation process of these devices, more applications should be used to develop a more comprehensive understanding of the research being provided by companies. More applications would affirm whether companies are relying specifically on traditional cigarettes to develop conclusions about their devices. By only using the Phillip Morris' application, I am limited to a single process for one type of e-cigarette device.

While the heatsticks of Phillip Morris' device do contain propylene glycol, a humectant found in e-liquids, many of the e-cigarettes marketed have a variety of flavors and formulas that contain a larger number of liquid components, which would certainly impact the research that is required. When heated, the e-liquid undergoes a phase change, going from liquid to vapor. Thus, companies would need to determine whether the vapors return to liquid when exposed to the temperature of the body. They would also have to show how these particles interact with the body in both the vapor and liquid form. Within the Phillip Morris application, there were three heatstick: Marlboro, smooth menthol and fresh menthol. The research for each heatstick was done separately, however, to make a direct comparison of the two the experiments should have been conducted together. The conclusion was that the flavor had no impact on the study, however, that is contradictory to a recurring idea within the literature.

The research in this thesis was further limited by the redactions within the PMTA application. Sections containing information about the engineering of device were marked, limiting my ability to examine evidence concerning the device. This could potentially impact my

analysis, because it restricts the information that can be used to justify the safety of the THS 2.2 Menthol device.

CHAPTER 5C: RECOMMENDATIONS

Overall, the process for the evaluation of e-cigarettes is very broad. The companies are responsible for providing information they deem relevant. Thus, there is no standard for what research is required. Within the PMTA, there was hesitancy by the Center for Tobacco Products to accept some of the experimental research that was included. There was also uncertainty regarding whether the methods for sample collection within the experiments would impact the results of studies. Although companies are responsible for providing research, the CTP should develop acceptable tests or at least guidelines for what needs to be shown, especially in the areas of research.

One part of the process that should be altered is the labeling and the determination of potential users. The data from Phillip Morris indicated that youth interactions with this device were low. However, an overwhelming number of youths have become e-cigarette users. The FDA should require marketing research where either companies or the FDA host a meeting with a variety of individuals to see the prevalent opinions being made about the device for all groups, including children. This would help discover potential users and help companies learn what characteristics of their products need to be altered to lower their appeal to youth. In addition to the likelihood of use study, Phillip Morris relied on areas where their device was already marketed to help affirm the notion that the likelihood of youth use would be lower. Although the evidence could be persuading, these places, like Japan, have different cultures than the United

States; thus, they cannot be used to accurately model or predict what would happen in the United States.

Another recommendation would be to increase the availability and accessibility of information for PMTAs. Transparency not only allows the government to be accountable, but also allows the public to understand processes that are in place to protect them. Lack of transparency can impact the relationship between the public and government, creating mistrust and restlessness towards the government. The inability to gather information about PMTAs impacts the analysis of this thesis. It limits not only what I was able to find, but also what I was conclude. The inability to gather information also impacts the information being reported on the FDA website. When looking into the different pathways of process, there were tables responsible for tracking the frequency of pathways used by companies, however, these tables were unable to depict the breakdown of the type of product. This emphasizes the need for more information because how would individuals know whether type of product a company makes impacts the pathway it would use. This would be helpful in showing whether e-cigarettes or traditional cigarette companies favor one pathway over the others.

In order to increase transparency, there should be more information available for monitoring the regulation process. One way to accomplish this would be to create a database that includes e-cigarette products involved with the regulation process. This would be helpful in illustrating whether companies are approved and whether they are in the process of approval allowing individuals to know more about the products they are using.

In addition to the accessibility of information, the process of enforcing the regulation for e-cigarettes needs to be improved. A multitude of e-cigarette products did not undergo the regulation process, yet they were still being sold on the market. By allowing these products to be

marketed without approval, the FDA allowed companies to bypass the regulation process and to introduce potentially harmful products onto the market. This means that e-cigarette companies were not held accountable for the products that they were producing for consumers.

In July of 2019, the courts mandated the FDA to issue a deadline for marketed e-cigarette products that would require companies to submit a PMTA by May 12, 2020. Due to the COVID-19 pandemic, this deadline for the PMTAs was further postponed until September. This mandate, however, does not provide an optimal solution because companies are still able to market their device up to one year while their applications are under review by the FDA. Ultimately, this allows the public to still interact with devices that have not been deemed safe for consumer use. In order to decrease the threat of these devices, e-cigarettes that have not received a marketing order should be taken off the market, especially if they were placed on the market after the FDA received the power to regulate electronic cigarettes. If companies are allowed to continue marketing their devices, the system created to regulate these devices would be contradicted. These devices were not supposed to be marketed until receiving a market order from the FDA, which did not occur. Thus, allowing e-cigarette devices to stay on the market decreases the enforcement of the regulation process.

Another area that should be focused on is the flavoring of e-liquids, which is the greatest obstacle against deterring youth from e-cigarettes. There are a multitude of flavors, like candy, that entice children to use these products. Flavors have been associated with the perception of less risk; thus, more needs to be done in order to provide a solution. Prior to the federal flavoring ban, states and local governments were enacting flavor bans to protect their constituents against the products. These actions helped initiate the federal ban on that went into effect in February 2020. This is probably the most effective way to prevent children from using e-cigarettes,

however, there are children who have already become consistent users. In order to show the children who already have been affected the risks, more research needs to be done to determine the mechanisms that make these devices dangerous so that the public can be aware of the all the risks associated with using e-cigarettes. Also, the information can be used in the current campaigns that are used to dissuade youth from using these products.

Although these devices are not used for medical purposes, the design of e-cigarettes are similar to the medical devices that deliver substances to individuals. Due to the complexities of its design, e-cigarettes seem more comparable to medical devices than traditional cigarettes. E-cigarettes are regulated the same as cigarettes because they include nicotine, however, most of the tobacco products under this regulation have simplistic designs. The evaluation of these process does not account for the intricacies associated with technology within the systems of e-cigarettes. The research has to account for more than what is provided for traditional cigarette, which is the limitation of the research included in the PMTA. In order to improve the process, more research needs to be done to understand interactions of the devices within all levels of the system.

The improvement of the PMTA surrounds increasing the validity and quality of research. The broadness of the current process gives too much control to the companies, which allow them to pick and choose what evidence they provide. By requiring guidelines around research, the FDA can strengthen its expertise while holding companies more accountable for what they include in their PMTA. Another way to improve the process is to implement some of characteristics of the process for the regulation of Class II and Class III medical devices, which undergo a high level of scrutiny by the Center for Devices and Radiological Health. This can

allow insight from technical expertise, which focuses on the entire system rather focusing on the delivery of the nicotine.

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APPENDIX

Appendix 1: Denial for the request of additional PMTAs

March 11, 2020

Request Number: 2020-2067

Sandra Rothenberg
Muckrock News
411A Highland Ave; Dept. MR 88962
Somerville, MA 02144

Subject of Request: Electronic cigarettes PMTA and SE's 2018 and 2019

Dear Sir/Madam:

The Food and Drug Administration (FDA) has completed processing your request for records under the Freedom of Information Act (FOIA).

I can neither confirm nor deny the existence of records that would be responsive to your request, as they would reveal confidential commercial information. Such information is prohibited from public release pursuant to Exemption 4 of the FOIA and 21 CFR 20.61(b)(c).

FDA's Regulations at CFR Part 20 are available at:
http:www.access.gpo.gov/nara/cfr/waisidx_04/21cfr20_04.htm.

You have the right to appeal this determination. By filing an appeal, you preserve your rights under FOIA and give the agency a chance to review and reconsider your request and the agency's decision. Your appeal must be mailed within 90 days from the date of this response, to: Agency Chief FOIA Officer, U.S. Department of Health and Human Services, Office of the Assistant Secretary for Public Affairs, Room 729H, 200 Independence Avenue, S.W., Washington, DC 20201; e-mail FOIARequest@PSC.hhs.gov. Please clearly mark both the envelope and your letter "**FDA** Freedom of Information Act Appeal."

If you would like to discuss our response before filing an appeal to attempt to resolve your dispute without going through the appeals process, please contact **Katherine Uhl at 301-796-8975**. You may also contact the FDA FOIA Public Liaison for assistance at: Office of the Executive Secretariat, US Food & Drug Administration, 5630 Fishers Lane, Room 1050, Rockville, MD 20857, E-mail: FDAFOIA@fda.hhs.gov

If you are unable to resolve your FOIA dispute through our FOIA Public Liaison, the Office of Government Information Services (OGIS), the Federal FOIA Ombudsman's office, offers mediation services to help resolve disputes between FOIA requesters and Federal agencies. The contact information for OGIS is as follows: Office of Government Information Services, National Archives and Records Administration, 8601 Adelphi Road–OGIS, College Park, MD 20740-6001; telephone at 202-741-5770; toll free at 1-877-684-6448; or facsimile at 202-741-5769; e-mail at ogis@nara.gov.

U.S. Food and Drug Administration
5630 Fishers Lane, Room 1035
Rockville, MD 20857
www.fda.gov

Appendix 1 (cont.):

If you have any questions, please contact Katherine Uhl at 301-796-8975.

Sincerely yours,

Sarah B. Kotler -S

Digitally signed by Sarah B. Kotler -S
Date: 2020.03.11 08:29:08 -04'00'

Sarah Kotler
Director
Division of Freedom of Information