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Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket Nos. FDA-2010-D-0635, FDA-2011-D-0147 and FDA- 2010-N-0646

Comments in Response to Submissions of Other Parties on Demonstrating Substantial
Equivalence for Tobacco Products

The American Cancer Society Cancer Action Network, American Heart Association, Legacy, American Lung Association, and the Campaign for Tobacco-Free Kids submit these comments regarding the standards FDA should apply in determining whether to grant or deny applications submitted pursuant to Section 905(j) of the Tobacco Control Act for designation of a new tobacco product as “substantially equivalent” to a predicate tobacco product. FDA has promulgated draft guidance on demonstrating substantial equivalence for tobacco products (Docket No. FDA-2010-D-0635); a second draft guidance on the same subject in the form of responses to frequently asked questions (Docket No. FDA-2011-D-0147); and a draft regulation on exemptions from substantial equivalence requirements (Docket No. FDA 2010-N-0646). The undersigned groups submitted comments in all three of those dockets.¹ In addition, FDA has held two webinars to describe its procedures for considering applications for substantial equivalence.² Tobacco product manufacturers also submitted extensive comments in all three of those dockets and the purpose of these comments is to respond to arguments made by the tobacco product manufacturers in those submissions.

¹ Copies of these comments are attached as Exhibits A, B, and C hereto.

² Webinars held on April 24, 2012 and August 21, 2012.

<http://www.fda.gov/TobaccoProducts/Labeling/TobaccoProductReviewEvaluation/NewTobaccoProductReviewandEvaluation/SubstantialEquivalence/ucm304518.htm>

TABLE OF CONTENTS

Executive Summary	5
I. Background and Introduction	11
A. Industry’s use of new tobacco products before the Tobacco Control Act	11
1. Introduction of new products to allay concerns about the health risks of smoking.	12
2. Introduction of new and modified products to make cigarettes more addictive.....	14
3. Product changes that increase the toxicity of cigarettes.	18
4. Modifications to tobacco products have increased initiation and discouraged cessation even if they do not increase the toxicity or abuse liability of the product.....	19
5. Consequences of permitting tobacco companies to modify existing products or introduce new products without premarket review.....	22
B. Findings and purposes of the Tobacco Control Act.	23
C. The statutory standard for the granting of new product applications.....	25
D. Tobacco products demonstrated to be substantially equivalent to a predicate product.....	26
II. Legal standards for the consideration of substantial equivalence applications	28
A. The statute places the burden of proving each and every element of substantial equivalence on the tobacco product manufacturer.	28

B. The statutory standard stating that characteristics of a new product be “the same” as the characteristics of the predicate product has a quantitative as well as a qualitative dimension and the words of the statute should be given their literal meaning.	34
C. The “same characteristics” analysis must include smoke constituents.....	35
D. Increases in the likelihood of initiation by nonusers and decreases in the likelihood of cessation by existing users are “questions of public health” as that term is used in the definition of “substantial equivalence.”.....	37
E. Tobacco product manufacturers must demonstrate that modifications to a tobacco product are not likely to increase initiation of tobacco use, particularly by youth, even where the modification increases neither the toxicity nor the abuse liability of the product.....	40
F. Congress did not intend the regulatory requirements for establishing substantial equivalence for tobacco products to be the same as the regulatory requirements for establishing substantial equivalence for medical devices.	44
1. The statutory language of the two sections is not the same.	44
2. The legislative history confirms that Congress recognized that differences between devices and tobacco products require different regulatory approaches and gave FDA discretion in enforcing the tobacco provisions.	48
G. A tobacco product must be found substantially equivalent to a single predicate product in order to justify the granting of a substantial equivalence application. .	50
H. A change in the name of a product makes the product a new product.	53
I. Any change in a product constitutes a modification.....	55
J. Use by a manufacturer of another manufacturer’s product as a predicate product.	55

III. Scientific evidence proffered by the industry does not show that increased levels of harmful or potentially harmful constituents do not raise different questions of public health.....56

 A. The standard proposed by Reynolds misrepresents what is scientifically known and distorts how scientific evidence is appropriately interpreted.56

 B. The studies cited by the tobacco companies do not provide support for the conclusion that changes in the levels of ingredients have no effect on disease risk.62

 C. Internal product evaluation programs of the companies do not provide credible judgments regarding substantial equivalence.66

 D. The existing ingredient reporting system under FCLAA provided no protection to consumers.68

 E. Tariff classifications provide no basis for a finding of substantial equivalence....69

 F. Arguments based on the specifications for predicate products do not provide a basis for the grant of an application for substantial equivalence.69

 G. Establishment of “good manufacturing practices” is no substitute for effective implementation of rigorous requirements for substantial equivalence.70

IV. Arguments regarding the testing of products.....71

 A. Machine testing provides useful information in the evaluation of substantial equivalence.71

 B. Alleged lack of laboratory capacity.72

 C. Alleged lack of validated methods of analysis73

D. Alleged inconsistencies in reporting requirements between Section 904 and Section 905(j).....	73
E. Proprietary blends and additives purchased from third parties.....	74
F. Insufficiency of samples for testing.....	75
V. Changes in the product to ensure consistency	75
A. Changes in tobacco blends.....	76
B. Changes in additives to maintain consistency	77
C. Changes in product design to maintain consistency	78
D. Summary of arguments on modifications to preserve consistency.....	78
VI. Relationship to regulations on minor modifications.....	79
VII. FDA should make more information available to the public regarding substantial equivalence applications	81

EXECUTIVE SUMMARY

Product modification in the tobacco industry has made tobacco products more deadly, more addictive, and more attractive to consumers. Moreover, sophisticated consumer research and product design by the major tobacco companies has led to tobacco products that increase youth initiation. The exhaustively documented findings of the United States District Court for the District of Columbia demonstrate that the major tobacco companies deliberately designed products to increase abuse liability and to facilitate experimentation and initiation by adolescents.³ They did so with complete disregard for the deadliness of their product. There is evidence that in the past several decades American cigarettes have become even more likely to

³ U.S. v. Philip Morris, USA, Inc., 449 F. Supp. 2d (D. D.C. 2006) 1, 565-616 (summarizing findings with regard to marketing to youth; 309-315 (summarizing findings with regard to manipulating the delivery of nicotine); 399-426 (summarizing findings with regard to making false health claims about new and modified products), *aff'd in relevant part*, 556 F. 3d 1095 (D.C. Cir. 2009), *cert. denied*, 130 S.Ct 3501 (2010).

cause lung cancer.⁴ The major tobacco companies also used product modification and diversification to develop and promote products to persuade consumers that such products were safer while knowing that such products were not.⁵

The Family Smoking Prevention and Tobacco Control Act of 2009 (“Tobacco Control Act”) is designed to put a stop to these practices. In the statute the Congress made detailed findings stating the reasons for the substantive provisions it enacts. Furthermore, it gave FDA broad authority to regulate tobacco products. FDA was given authority to set standards for tobacco products. For the first time, tobacco companies were required to measure and report to FDA all the ingredients in their products and all the harmful and potentially harmful constituents in tobacco smoke. Moreover, tobacco companies were prohibited from introducing new tobacco products or modifying existing products unless FDA grants a premarket application permitting them to do so upon a showing by the manufacturer that the marketing of the product is appropriate for the protection of the public health. These provisions are designed to change the practices of the tobacco product manufacturers whose actions created the tobacco epidemic. They are designed to prohibit product modification from being the vehicle through which tobacco companies addict more adolescents to products that will kill them or to make it harder for tobacco users to quit or to increase the risk of any disease to a tobacco user. Congress made it clear in its legislative findings that protection of the public health is the overarching statutory goal. The new product requirements of the Act are essential provisions to accomplish this goal.

The substantial equivalence provisions of the Act provide an alternative to the new product standards if the manufacturer is able to demonstrate that the product has the same characteristics as a product that was commercially marketed on February 15, 2007 or does not raise a different question of public health. Under the substantial equivalence provisions, a tobacco product manufacturer may file an application demonstrating that a new tobacco product (i.e., a product that was not commercially marketed on February 15, 2007 or a modification of a product that was commercially marketed on that date) is “substantially equivalent” to a product

⁴ Burns DM, Anderson CM, and Gray N, Has the lung cancer risk from smoking increased over the last fifty years?. *Cancer Causes Control* 22:389-97 (2011).

⁵ U.S. v. Philip Morris, 449 F. Supp. 2d, 1, 560-561; U.S. Department of Health and Human Services, National Institutes of Health, Risks Associated with Smoking Cigarettes with Low-Machine-Measured Yields of Tar and Nicotine (2001) (hereinafter “Monograph 13”).

was commercially marketed on that date (a “predicate product”). If the new tobacco product was commercially marketed by March 22, 2011 and a substantial equivalence application was filed by that date, the product may stay on the market unless and until FDA denies the application. If the new tobacco product was not marketed until after that date or if the application was not filed until after that date, the product may not be commercially marketed until FDA grants the application. It is clear, however, that Congress did not intend the substantial equivalence provisions to permit manufacturers to market new or modified products unless the manufacturer could demonstrate that such products did not increase the risk to the public health over that presented by the predicate product.

Tobacco product manufacturers have tried to use the substantial equivalence provisions of the Act to subvert and nullify the new product requirements. As of August, 2012, they had filed nearly 3,500 substantial equivalence applications—and not a single new product application. According to the tobacco industry, every single product introduced or planned for introduction since February 15, 2007 is substantially equivalent to one or more products marketed on that date. Moreover, almost 90 percent of these applications were filed by March 22, 2011 so that the new products covered by them remain on the market unless and until FDA denies the application. Tobacco product manufacturers are trying to use the substantial equivalence provisions to continue marketing new products just as they have done in the past. To date, FDA has not taken final action on any of the nearly 3,500 substantial equivalence applications.

The tobacco industry’s misuse of the substantial equivalence application process threatens to nullify the public health protections enacted by the Tobacco Control Act. If the positions advocated by the industry are adopted by FDA, tobacco companies will be permitted to use product modification to develop more and more sophisticated products to appeal to and addict new tobacco users and make it harder for current users to quit.(Sec. I)

II. Legal Standards

The Tobacco Control Act clearly puts the burden of proof on the tobacco product manufacturers to demonstrate each and every element of substantial equivalence. The tobacco companies, while not openly contesting this issue, have argued for standards that in effect shift

the burden to FDA to prove that new tobacco products do not meet the statutory requirements. FDA should recognize and reject these arguments. In a context in which we know that tobacco products are deadly and addictive but we do not know all the mechanisms by which these products do their damage, allocation of the burden of proof for regulatory decisions is of the highest importance. (Sec. II A)

The statutory language for finding that the characteristics of a new product are “the same” as those of the predicate product should be given its literal meaning and the characteristics of a tobacco product includes smoke constituents. Adopting the companies’ arguments on these issues would prevent FDA from effectively preventing products that may be more addictive or more lethal from being marketed. (Sec. II B-C)

Increases in the likelihood of initiation by non-users and decreases in the likelihood of cessation by existing users are “questions of public health” as that term is used in the definition of substantial equivalence. A more narrow definition of what constitutes “questions of public health”, such as those proposed in various industry comments, would fail to give consumers the protection the statute was intended to provide. (Sec. II D)

In determining whether a new tobacco product is “substantially equivalent” to a predicate product, a manufacturer should be required to demonstrate that the product is not likely to increase the initiation of tobacco use, particularly among adolescents, even if the modification in the product increases neither the toxicity nor the abuse potential of the product. Contrary to the companies’ contentions, they have intensively studied potential product markets and designed products to appeal to narrow submarkets. They have developed products that increase the likelihood that adolescents will initiate tobacco use. The extensive findings made by the Tobacco Products Scientific Advisory Committee regarding menthol cigarettes demonstrate these practices. (Sec. IIE)

Contrary to the arguments of the tobacco companies, Congress did not intend the regulatory requirements for establishing substantial equivalence for tobacco products to be the same as those for medical devices. Congress recognized that medical devices are intended to improve the health of consumers and therefore that their development should be encouraged. The

opposite is true for tobacco products. This is demonstrated by the language of the statute and by the legislative history. (Sec. II F)

Contrary to the arguments of the tobacco companies, a tobacco product must be found substantially equivalent to a single predicate product in order to justify the granting of a substantial equivalence application. The position taken by the tobacco companies would permit a product to be found substantially equivalent even it combined the most dangerous of elements of every existing product or if it resulted in a different combination of chemicals without proof of the impact of the change. (Sec. II G)

III. Arguments about scientific standards

The standard proposed by R.J. Reynolds misrepresents what is scientifically known and distorts how scientific evidence is appropriately interpreted.⁶ The companies have not—and cannot—demonstrate that the levels of toxic or carcinogenic constituents in tobacco products do not affect disease risk. Nor can the companies demonstrate that commonly used additives do not affect the abuse potential of tobacco products. The evidence is strongly to the contrary. Additives and product design do affect the addictiveness of tobacco products and manufacturers have manipulated products to increase addictiveness. In addition, none of the studies presented by the companies demonstrates that changes in the level of ingredients or product design have no effect on disease risk. (Sec. III A-B)

Arguments by the companies that their internal evaluation programs provide sufficient assurance to demonstrate substantial equivalence have no credibility in light of the exhaustively documented record of misrepresentations and suppression of scientific evidence by the industry over the course of many decades and continuing into the present. (Sec. III C)

Arguments based on the specifications for predicate products do not provide a basis for the grant of an application for substantial equivalence. (Sec. III E)

IV. Arguments regarding the testing of products

⁶ Comments of R.J. Reynolds Tobacco Corp. in FDA-2010-N-0646 at 33-35 (March 21, 2011).

The tobacco product manufacturers argue that the results of machine testing should not be used in evaluating applications for substantial equivalence. However, although machine testing by itself is not sufficient to demonstrate the risks of tobacco products as they are actually used, machine testing provides essential information in the evaluation of substantial equivalence. All the harmful and potentially harmful constituents in tobacco products can and should be measured for purposes of establishing substantial equivalence. (Sec. IV A)

The arguments of the companies regarding alleged lack of laboratory capacity, lack of validated modes of analysis, differences in reporting requirements between section 904 and section 905(j) of the Act, difficulty of testing proprietary blends and additives purchased from third parties, and insufficiency of samples for testing do not demonstrate reasons why test results should not be required. (Sec. IV B-F). If anything, it demonstrates that the companies have not been doing what is necessary to understand and present adequate scientific evidence to meet the new statutory standard.

It is relevant to recognize that far less scientific knowledge about tobacco products is available to FDA today because the tobacco industry has concealed information about the way products have been modified and designed in the past. To protect the public, FDA has to require the industry to do all necessary testing according to standards established by FDA.

V. Changes in the product to ensure consistency

Arguments made by the companies that changes that are allegedly required and involving blends of different tobaccos, changes in additives, and changes in product design to ensure consistency do not provide a justification for disregarding potential increases in the toxicity, carcinogenicity, or abuse liability of a tobacco product in determining substantial equivalence. Similarly, product changes, allegedly to ensure product consistency, should not be permitted if the manufacturer cannot demonstrate that they will not increase initiation of tobacco use by non-users.

VI. Relationship to regulations on minor modifications

FDA should be very cautious in establishing exemptions for “minor modifications.” Classification of a modification as “minor” has the potential to remove entire categories of product changes from effective premarket scrutiny and thus is highly susceptible to abuse by tobacco manufacturers seeking to evade regulatory requirements. It is understandable that FDA would require regulatory experience evaluating data submitted in connection with substantial equivalence applications before concluding that a category of modifications should be exempted from these regulatory requirements.

VII. FDA should provide more information to the public regarding substantial equivalence applications.

It is important for the public to be informed about FDA’s evaluation of substantial equivalence applications. The existing practice effectively prevents any public understanding of the way such applications are being evaluated. Moreover, FDA has not availed itself of expert advice from outside the agency that could inform its decision-making process.

TEXT OF THE COMMENTS

I. BACKGROUND AND INTRODUCTION

A. The industry’s use of new tobacco products before the Tobacco Control Act

In order to understand the reasons for the statutory changes made by the Tobacco Control Act and to formulate rules to implement them, it is necessary to understand the practices of the industry before the enactment of the statute with regard to the introduction of new products and the results of those practices. Prior to the enactment of the Tobacco Control Act, tobacco product manufacturers were free to modify existing products and introduce new products without regulatory constraint and without any obligation to disclose to any regulatory authority or the public what the contents of their products were or what changes were being made to the products. In the decades preceding the enactment of the Tobacco Control Act, manufacturers introduced thousands of new cigarette brands and subbrands. These new products were carefully designed and marketed to address the particular preferences of customers and potential

customers—including attracting adolescents as new users and making it easier for adolescents to start.⁷ Numerous elements regarding the tobacco product could affect consumer acceptance and uptake by new users and a broader range of new users. All elements of the product were designed with meticulous care to optimize consumer acceptance. This care extended not only to the tobacco blend, but also to additives and other elements of the product, including the filter, ventilation holes, paper, casing, moisture content, product configuration (e.g., weight, length, etc), and other product features. American tobacco manufacturers developed at least 599 additives.⁸ These additives, among other things, affected the taste of the cigarette, the perceived smoothness of the smoke, and the overall experience of the smoker in a manner designed to result in expanding the market, attracting new users and repeated product purchases. Additives performed this function whether or not they were present in the product in levels sufficient to constitute “characterizing flavors.” Additives such as chocolate and menthol played important roles in shaping the smoking experience even though these flavorings could not be detected as characterizing flavors.⁹ None of this occurred by accident. However, the tobacco industry has never been required to disclose the research and testing that preceded these product changes.

1. Introduction of new products to allay concerns about the health risks of smoking.

The introduction of new tobacco products has played an extremely important strategic role in allaying consumers’ fears about the health effects of smoking. In the 1950s, following the first major release of information about the negative health effects of smoking, tobacco companies responded with hundreds of new tobacco products—most prominently introducing a huge variety of filters—designed to persuade smokers and potential smokers concerned about the health effects of smoking that the new and modified tobacco products were safer than the cigarettes they had previously been smoking.¹⁰ Virtually without exception, these

⁷ U.S. v. Philip Morris, 449 F. Supp. 2d 1, 334-338; Tobacco Products Scientific Advisory Committee (TPSAC), Menthol Cigarettes and Public Health: Review of the Scientific Evidence and Recommendations, July 2011. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM269697.pdf>

⁸ Rabinoff M, Caskey N, Rissling A, Park C, Pharmacological and Chemical Effects of Cigarettes, Amer. J. of Public Health, vol. 97, no. 11 at 1981 (Nov. 2007).

⁹ World Health Organization, Study Group on Tobacco Product Regulation (“TobReg”), Report on the Scientific Basis of Tobacco Product Regulation (2012) at 17.

¹⁰ Monograph 13 at 5.

representations had no basis in fact.¹¹ By misrepresenting the health effects of newly introduced filter cigarettes and by promoting a succession of products with modified filters, tobacco companies successfully persuaded millions of smokers not to quit and millions more than they could safely initiate smoking.

Later, in the 1960s, 1970s and 1980s, tobacco companies introduced new and modified products such as “light” cigarettes, accompanied by claims that the cigarettes were lower in tar and nicotine and therefore less hazardous. These claims too were false—a fact known to the tobacco companies at the time they made them.¹² Consumers compensated for reduced presence of tar and nicotine in the rod by changing the way they smoked.¹³ Tobacco companies facilitated this compensation by designing cigarettes with ventilation holes in the filter. When smoked by machines, the cigarettes delivered lower levels of tar and nicotine. However, when smokers actually smoked them, they covered the ventilation holes with their fingers and the harmful smoke constituents delivered to consumers were no lower with light cigarettes than with other brands. The history of this remarkable misrepresentation is recounted in detail in NCI Monograph 13 and in the opinion of the United States District Court for the District of Columbia in *U.S. v. Philip Morris*, 449 F. Supp. 2d 1, 456-475 and is recited in summary form in the Congressional Findings of Fact in the Tobacco Control Act itself.¹⁴ In addition, the industry promoted menthol cigarettes as a safer alternative and many consumers began to smoke menthol cigarettes based on the erroneous belief that they were safer than non-menthol cigarettes.¹⁵ It was not just consumers who were fooled and left in the dark. Government, too, was fooled and did not understand the actual impact of the product changes.

¹¹ *U.S. v. Philip Morris*, 449 F. Supp. 2d 1, 430-431, 456. Monograph 13 at 146.

¹² *U.S. v. Philip Morris*, 449 F. Supp. 2d 1, 560-61.

¹³ *Id.*; Monograph 13 at 60.

¹⁴ Family Smoking Prevention and Tobacco Control Act of 2009 (“Tobacco Control Act”), P.L. 111-31, 21 U.S.C. § 387, Findings (38)-(39).

¹⁵ Tobacco Products Scientific Advisory Committee, *Menthol Cigarettes and Public Health: Review of the Scientific Evidence and Recommendations*, July 21, 2011 at 63.

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM269697.pdf>.

2. Introduction of new and modified products to make cigarettes more addictive.

Existing tobacco products have been modified to make them more addictive. In *U.S. v. Philip Morris USA, Inc.*, the Court made voluminous findings of fact, supported by overwhelming evidence, demonstrating that all the major tobacco companies had for decades manipulated the design of cigarettes to ensure a level of nicotine delivery in their cigarettes that would sustain addiction. The court summarized its conclusions

. . .[C]igarette company defendants researched, developed, and implemented many different methods and processes to control the delivery and absorption of the optimum amount of nicotine which would create and sustain smokers' addiction. These methods and processes included, but were not limited to: altering the physical and chemical make-up of tobacco leaf blends and filler; maintaining or increasing the nicotine to tar ratio by changing filter design, ventilation and air dilution processes, and the porosity and composition of filter paper; altering smoke pH by adding ammonia to speed nicotine absorption by the central nervous system; and using other additives to increase the potency of nicotine.

449 F. Supp. 2d, 1, at 383-84.

Numerous other studies have reached similar conclusions. A study by the Harvard School of Public Health in 2006 concluded that during the period 1997-2005 there had been a statistically significant increase in smoke nicotine yield in eight out of ten of the largest-selling brand families in the United States.¹⁶ The authors concluded that this outcome was produced both by increased nicotine in the tobacco rod and by other design modifications that, *inter alia*, increased the number of puffs per cigarette.

Moreover, cigarette companies have used additives to increase the addictiveness of cigarettes. An authoritative expert study group of the World Health Organization concluded in a 2012 report that “the industry actively investigated the effects of nicotine and other substances

¹⁶ Harvard School of Public Health, Connolly GN, Alpert HR, Wayne GF, Koh H, Trends in Smoke Nicotine Yield and Relationship to Design Characteristics in Popular United States Cigarette Brands, 1997-2005. This conclusion is consistent with sworn testimony of a former Philip Morris employee stating that the company pursued a policy of increasing the level of nicotine delivered to smokers to promote addiction. *Id.* at n. 25 (citing testimony of William Farone).

on the nervous system in an effort to increase the addictiveness. . .of their products.”¹⁷ The Committee found

The approaches used by the tobacco industry included manipulation of the nicotine dosing capacity of its products, products designed to increase the speed of nicotine delivery and hence its addictive ‘impact’ or ‘kick’. Control of tobacco and smoke pH to increase the unprotonated (‘free base’) fraction of nicotine in the smoke, control of smoke particle size to increase lung penetration efficiency, product engineering to increase stimulation of the trigeminal nerves of the oral cavity and upper airways, and the use of a broad range of chemical additives to make smoke feel smoother, cooler and more pleasant, in order to facilitate deep inhalation and the transition to addiction.¹⁸

Tobacco companies have added ammonia compounds to cigarettes in order to speed the delivery of free nicotine to the brain.¹⁹ There is voluminous evidence that tobacco companies discovered this relationship as early as the 1960s and have used additives in order to increase the alkalinity of smoke and thereby increase the addictiveness of the product.²⁰ A 1965 internal BAT memorandum concludes “nicotine transfer has increased as a result of ammonia treatment.”²¹ In addition, manipulation of pH to modify buffering chemicals in smokeless products is a key to manipulating the nicotine delivery of such products, with the intent of developing and maintaining dependence.²² Moreover, the exploitation of “free nicotine” and its enhanced effects helped cigarette companies find ways to deliver high doses of nicotine to smokers while registering low tar readings on the FTC machines.²³

A 2007 study of cigarette additives concluded that more than 100 of 599 documented cigarette additives have pharmacological actions that camouflage the odor of environmental

¹⁷ World Health Organization, Study Group on Tobacco Product Regulation (“TobReg”), Report on the Scientific Basis of Tobacco Product Regulation (2012)

¹⁸ Id.

¹⁹ Bates C, Jarvis M, Connolly GN, Tobacco Additives, Cigarette Engineering and Nicotine Addiction, 1999.

²⁰ A 1992 internal Brown & Williamson memorandum, identifies “ammonia technology” as the “key factor” in the world-wide success of the Marlboro brand. B&W, October 26, 1992, Minn. Trial Exhibit 10110, cited in Bates, et al. at 3.2.

²¹ BAT memorandum, May 17, 1994, FN B2107 BN105454359-4346 The Effect of Additives on Smoke Chemistry.

²² TobReg (2012) at 16.

²³ Bates, supra, at 3.3. The methodology for this evasion was summarized succinctly by former Philip Morris employee William A. Farone: “...[I]f you don’t take into account the gas phase, if I . . .increase the pH and the smoke drops so that I can put more of the nicotine from the liquid into the gas and I am not measuring the gas, then in fact, you don’t measure that nicotine which gets in the gas phase. This has been known since the late 1960s and early 1970s.”

tobacco smoke emitted from cigarettes, enhance or maintain nicotine delivery, could increase the addictiveness of cigarettes, and mask symptoms and illnesses associated with smoking behaviors.²⁴ The article cites sophisticated studies done by Philip Morris in the 1980s that demonstrated a systematic relationship between increases in filler pH and increases in gas phase nicotine.²⁵ The article contains an extensive list of possible pharmacological effects of selected chemical additives.²⁶ It concludes that “from a public health perspective, increasing the addictive potential of cigarettes with additives (e.g., via formulas including sugar, sorbitol, and DAP) increases the likelihood that smokers will become addicted and that current smokers will have more difficulty quitting. Consequently, there will be greater levels of morbidity and mortality associated with smoking....Unregulated use of additives in tobacco products subjects billions of smokers and nonsmokers alike to an uncontrolled experiment with potentially devastating health effects.”²⁷

Cigarette companies have added sugars to their products, which upon burning are converted into acetaldehyde and other aldehydes. In addition to being carcinogenic, acetaldehyde also increases the speed of delivery of nicotine to the brain.²⁸ A report by a group of expert scientists prepared to inform product regulation by the European Union contains a table showing that tobacco has a substantially higher risk of causing addiction than heroin, cocaine, alcohol, or cannabis.²⁹ Moreover, the report concludes that additives contribute to this high level of addictiveness: “[A]part from naturally occurring substances in tobacco leaves, a number of ingredients in the final product may create or increase dependence.”³⁰ The Report reaches the following conclusions.

“...Sugars, polysaccharides and cellulose fibres which are naturally present in tobacco, or sugars added in high quantities to most tobacco products, give rise to numerous aldehydes, such as acetaldehyde, in tobacco smoke. Acetaldehyde given intravenously is self-administered and enhances the addictiveness of nicotine in experimental animals. Additives that facilitate deeper inhalation (e.g.,

²⁴ Rabinoff M, Caskey N, Rissling A, and Park C, Pharmacological and Chemical Effects of Cigarette Additives, 97:11 American Journal of Public Health, pp. 1981-1991, November 2007.

²⁵ Id. at 1983.

²⁶ Id. at 1984-85.

²⁷ Id. at 1987-88.

²⁸ Scientific Committee on Emerging and Newly Identified Health Risks (“SCENIHR”), Addictiveness and Attractiveness of Tobacco Additives (2010) at 42-43.

²⁹ SCENIHR at 15, Table 1.

³⁰ SCENIHR at 15.

menthol) or inhibit the metabolism of nicotine may enhance the addictiveness of nicotine activity.”³¹

The Report also concludes that

“In addition to the interactions between additives and constituents of tobacco, the burning of tobacco creates other complex chemical substances that may be toxic or favour addiction. An example of this is aldehydes, such as acetaldehyde formed by the pyrolysis of various sugars and polysaccharides in the tobacco.”³²

Philip Morris argues that statements in the SCENIHR Report support its assertion that there is no “agreement about various possible endpoints which define whether an additive or a combination of additives increases the addictive potency or attractiveness of the final tobacco product.”³³ Philip Morris also cites a statement in the Report that the methods used to quantify the addictive potential of additives have limitations because of technical issues.³⁴ However, an examination of the full text of the SCENIHR Report demonstrates that a substantial body of data supports the conclusion that addition of sugars and ammonia compounds to cigarettes enhances their addictive potential. The fact that the available test procedures can be improved provides no justification for permitting the tobacco companies to expose the public to increased levels of substances that even plausibly could increase the addictiveness of the product. Once again, the question presented is whether, given a level of information that is substantial and credible, but not 100% complete, questions of public health are to be resolved by exposing consumers to increased levels of substances that evidence demonstrates may increase the likelihood of addiction or by preventing such exposure.

Similarly, there is credible evidence that other additives, such as laevulinic acid and urea, may contribute to smoke inhalation and dependence by making smoke feel smoother.³⁵ And there is evidence that physical design features may also contribute to dependence by making smoke easier to inhale and nicotine transfer to target receptors more efficient such as filter ventilation and smoke particle size. In addition, cocoa, which is widely used as an additive, contains alkaloids which evidence indicates may modify the effects of nicotine and have an

³¹ *Id.* at 4.

³² *Id.* at 16.

³³ Comments of Philip Morris, USA, Inc. and US Smokeless LLC in FDA-2010-N-646 at 5 (March 22, 2011).

³⁴ *Id.*

³⁵ TobReg (2012) at 17; Bates at 3.4.2

independent pharmacological effect. Cocoa also contains theobromine, a substance that dilates the airways and thus facilitates increased smoke and nicotine intake.³⁶ A similar effect is produced by another additive, glycyrrhizin, an ingredient of licorice.³⁷

It is the position of the tobacco companies that no regulatory action is appropriate unless there is conclusive proof that an additive increases the addictiveness of the product. Such a conclusion in effect puts the burden on FDA to demonstrate conclusively that an additive increases addictiveness as a basis for denying a substantial equivalence application. However, the statute appropriately puts the burden on the tobacco product manufacturer to demonstrate that the additive does not increase addictiveness. Where there is scientific evidence indicating a plausible possibility that substances increase the addictiveness of the product, tobacco product manufacturers cannot be deemed to have carried their burden. A product containing ammonia compounds or sugar additives at levels higher than the predicate product should not be found to be substantially equivalent to the predicate product.

3. Product changes that increase the toxicity of cigarettes.

American cigarette companies have adopted product designs that may have increased the deadliness of cigarettes. A carefully designed study published in 2011 concluded that lung cancer risks from smoking have increased over the past fifty years.³⁸ The study concluded that the results obtained

“... support the hypothesis that lung cancer risks from smoking may be increasing in the U.S. due to changes in cigarette design, and correspondingly that regulatory control over cigarette design may have the potential to reduce the risk of smoking.”³⁹

The authors identified several potential explanations for these results, including the possibility that “increasing nitrosamine levels may make [cigarette] smoke more carcinogenic at

³⁶ Bates at 3.4.3.

³⁷ Id at 3.4.4.

³⁸ Burns DM, Anderson CM, and Gray N, Has the lung cancer risk from smoking increased over the last fifty years?. *Cancer Causes Control* 22:389-97 (2011).

³⁹ Id. at 397.

any level of exposure.”⁴⁰ Although the study is not conclusive, it provides evidence that product design may lead to changes in the disease risk and mortality resulting from cigarette smoking. Furthermore, these data contradict the simplistic and self-serving conclusion offered by tobacco companies that because all cigarettes cause death and disease all cigarettes should be considered substantially equivalent to one another. If there is any plausible basis for concluding that a cigarette may be more toxic than the predicate product, the new product cannot be considered to be substantially equivalent and validate the Congress’s decision to place the burden of demonstrating each and every element of substantial equivalence on the manufacturer.

4. Modifications to tobacco products have increased initiation and discouraged cessation even and if they do not increase the toxicity or addictiveness of the product.

Tobacco product manufacturers have made extensive use of product modifications to increase product initiation and discourage cessation. A principal vehicle for such modifications has been the introduction of additives that either impart characterizing flavors or mask harsh tobacco tastes that would discourage inexperienced users from initiating use.⁴¹ Such product modifications are of particular importance since the overwhelming majority of those initiators are adolescents. In recognition of the potential for such changes to influence youth initiation, the Tobacco Control Act prohibited the use of characterizing flavors, other than menthol, in cigarettes effective on June 22, 2009.⁴² The Act also called for the Tobacco Product Scientific Advisory Committee to study the use of menthol and report its findings to FDA as its first order of business.

TPSAC conducted an exhaustive study of the evidence concerning the use of menthol as a characterizing flavor in cigarettes and issued a massive report in July 2011.⁴³ After reviewing the evidence, TPSAC concluded that although menthol does not increase the toxicity of

⁴⁰ Id. The National Cancer Institute has observed that “changes in the agricultural, curing and manufacturing processes of cigarettes have resulted in an increase in tobacco specific nitrosamines in cigarette smoke that may have contributed to the increase in adenocarcinoma of the lung observed over the past several decades. Monograph 13 at 184 (2001).

⁴¹ Many other product modifications, such as changes in product design, changes in the filter, changes in the paper, and many others can affect the smoker’s sensory experience.

⁴² Tobacco Control Act, Sec. 907(a); 21 U.S.C. § 387g(a).

⁴³ Tobacco Products Scientific Advisory Committee, *Menthol Cigarettes and Public Health: Review of Scientific Evidence and Recommendations*, July 21, 2011.

cigarettes, it does increase youth tobacco initiation, the likelihood of addiction and the degree of addiction in young smokers.⁴⁴ The evidence cited by TPSAC came from numerous sources and demonstrates vividly how product modifications can have a profound effect on public health even if they do not increase the toxicity of the product.

TPSAC began by examining the physiological effects of menthol and concluded that it both imparted a pleasant minty taste and suggested both cooling and smoothing sensations. These sensations not only impart their own characterizing flavor, but they also mask the inherent harshness of tobacco smoke that otherwise makes smoking an unpleasant experience for those beginning to experiment with tobacco. TPSAC concluded that as a result of these sensory properties the introduction of menthol at carefully calibrated levels did in fact make it more likely that young people would initiate smoking and thereby become addicted. Moreover, it found that those young people who initiate using menthol cigarettes were more likely to become addicted and become long-term daily smokers.⁴⁵

Importantly, TPSAC found that the levels of menthol had to be carefully calibrated in order to optimize product acceptance. Use of menthol at high levels, rather than imparting a soothing sensation, exacerbates the harshness of the smoke and produces burning and irritation.⁴⁶ Thus, the products most successful in the market—and particularly in the youth market—were those with moderate levels of menthol. Tobacco product manufacturers were keenly attuned to this phenomenon and their cigarettes were designed in ways that take advantage of this insight.⁴⁷ Lorillard, the manufacturer whose cigarette brand most successfully accomplished this, saw its leading brand, Newport, become the second-largest selling brand in America, both with adults and with youth smokers.⁴⁸

Moreover, tobacco companies used extremely aggressive marketing programs to work in concert with product design to target populations to which such modified cigarettes would appeal.⁴⁹ The result has been a market in which nearly thirty percent of American smokers

⁴⁴ *Id.* at 215-216.

⁴⁵ *Id.*

⁴⁶ *Id.* at 23.

⁴⁷ *Id.* at 219.

⁴⁸ SAMHSA, Office of Applied Studies, National Survey on Drug Use and Health, 2004 and 2005.

⁴⁹ Tobacco Products Scientific Advisory Committee, “Menthol Cigarettes and Public Health, Review of the Scientific Evidence and Recommendations,” July 21, 2011 at 68-74.

smoke menthol cigarettes and in which the percentage of youth smoking menthol cigarettes is even higher.⁵⁰ TPSAC also cited evidence demonstrating that the prevalence of menthol is inversely proportional to the age of the users: the younger youth users are, the more likely they are to be menthol smokers and to have initiated experimentation with menthol cigarettes.⁵¹

These facts led TPSAC to conclude that “the availability of menthol cigarettes increases initiation and reduces cessation” and that “the removal of menthol cigarettes from the market would benefit the public health.”⁵²

TPSAC’s conclusions regarding the effect of menthol on youth initiation have important ramifications for development of a policy regarding substantial equivalence. It is clear that a change in the level of menthol in cigarettes can and does influence the use of the product by young people initiating tobacco use. Consequently, such a change would “raise a different question of public health” and a cigarette with a different level of menthol than a predicate product would not be substantially equivalent to the predicate product.

While menthol is the most extensively studied additive, it is by no means the only one that affects the sensory experience of smoking. In fact, tobacco companies use many hundreds of additives that do just this. The potential effect of all such additives is relevant to the statutory standard. It is important to note that such additives can affect the sensory experience of smoking without imparting a characterizing flavor to the cigarette or its smoke.⁵³ Thus, chocolate, for example, is frequently used to impart smoothness even if it cannot be detected as a characterizing flavor. An increase or decrease in the level of additives can affect the appeal of a tobacco product in ways that lead to increased initiation, more frequent tobacco use or decreased cessation. Thus, any change in the level of an additive in a cigarette potentially raises a different question of public health. In evaluating the effect of a change in the level of an additive, FDA should require production of all data the company possesses or controls relating to the effect of the changed level of the additive on consumer acceptance and, particularly, on smoking initiation. If a company has not collected such data, it should be required to do so. The burden of proving that such a change will have *no* effect on product initiation is on the manufacturer.

⁵⁰ *Id.* at 215, 218.

⁵¹ *Id.* at 215-216.

⁵² *Id.* at 220-21, 225.

⁵³ TobReg (2012), *Supra*, n. 5.

In all cases, what is relevant is the ultimate product and market studies of the product that reflect the interaction of all changes in product design. Accordingly, studies of the effect of increases or decreases in the level of an additive in isolation would not demonstrate the effect of such a change as it would appear in a product. It is conceivable that the interaction of numerous modifications might lead to a result that could not be predicted by looking only at a single modification. Thus, all modifications to product design, including but not limited to additives, are relevant.

Philip Morris has argued that changes in the levels of additives that are not toxic should be exempt from filing requirements for substantial equivalence.⁵⁴ For the reasons set forth above, this argument is wrong. Moreover, the same reasons that require rejection of Philip Morris's argument with regard to additives apply equally to all changes in product design and are not limited to changes in the level of additives. Since any changes in product design can influence the sensory experience of the smoker, any change in product design may raise a different question of public health.⁵⁵

5. Consequences of permitting tobacco companies to modify existing products or introduce new products without premarket review.

In the tobacco industry, product modification has too often made cigarettes more dangerous, more addictive and more appealing to non-smokers. Not only have the major tobacco product manufacturers deliberately designed their products to achieve these results, but they have falsely denied doing so. As the United States District Court found in *U.S. v. Philip Morris*,

. . . [T]he evidence is overwhelming that Defendants have, over the course of many years, time and again—and with great self-righteousness—denied that they

⁵⁴ Comments of Philip Morris USA, Inc. and U.S. Smokeless LLC in FDA-2010-N-0646-0011 at 6-7 (March 22, 2011).

⁵⁵ As the World Health Organization Study Group on Tobacco Product Regulation concluded in its 2012 report, “in apparent coordination with product designs intended to increase dependence potential, [product] design has also been used to increase the attractiveness of products to target populations.” These efforts have included the design, packaging and marketing of cigarettes to be particularly attractive to certain populations on the basis of gender, socioeconomic status and racial or ethnic affiliation. *TobReg* (2012) at 9-10. The SCENIHR Report also confirms the findings of many other reports that “the attractiveness of tobacco products may be increased by a number of additives that create a specific taste/flavor in order to attract certain target groups.” Report at 49. The Report also concludes that additives may be used to facilitate product design that makes cigarettes “easier to start smoking with.” By reducing and changing the harshness of the smoke, special target groups may be reached. *Id.*

manipulated the nicotine in cigarettes so as to increase the addiction and dependence of smokers. Those denials were false.

449 F. Supp. 2d at 384.

Moreover, the continued development and introduction of new and modified products that appeal to target subgroups in the general population and are heavily promoted to those groups has resulted in the addiction of large numbers of underage users. As the National Cancer Institute concluded,

“The tobacco industry has become increasingly sophisticated in applying marketing research to population segments in order to design products, messages, communication channels, and promotions more aligned with the needs and susceptibilities of particular market segments. This research results in more efficiency, greater reach, and increased effectiveness for marketing activities aimed at targeted populations.⁵⁶

Decisions regarding the implementation of a policy to guide substantial equivalence determinations should be informed by this history. Regulatory policy, informed by increased scientific knowledge and now, for the first time, by detailed information about the content of tobacco products and their smoke constituents, can and should put a stop to the product manipulation that has characterized and continues to characterize the conduct of the tobacco industry. The failure to adopt strict standards for determining substantial equivalence would permit tobacco product manufacturers to nullify the standards established by the statute for premarket authorization and continue to use product modification to addict consumers ever more effectively to increasingly attractive and deadly products.

B. Findings and purposes of the Tobacco Control Act

Standards for substantial equivalence should be consistent with both the language and the fundamental purposes of the Tobacco Control Act. When Congress enacted the Tobacco Control Act, it made specific findings as the basis for its legislative enactment and it specifically stated the purposes of the legislation. Congress found that tobacco use is the foremost preventable cause of premature death in America, causing over 400,000 deaths in the United States.⁵⁷ It

⁵⁶ National Cancer Institute, United States Department of Health and Human Services, *The Role of the Media in Promoting and Reducing Tobacco Use*, at 171 (2008).

⁵⁷ Tobacco Control Act, Finding (13).

found that that approximately 8,600,000 Americans have chronic illnesses related to smoking.⁵⁸ Moreover, it found that a consensus exists within the scientific community that tobacco products are inherently dangerous and cause cancer, heart disease, and other serious adverse health effects and that nicotine is an addictive drug.⁵⁹ Furthermore, it found that “it is in the public interest for Congress to adopt legislation to address the public health crises *created by actions of the tobacco industry.*”⁶⁰ (emphasis added)

Congress made it clear that it was providing the Food and Drug Administration with far-reaching authority to regulate tobacco products because of its substantial scientific expertise in “identify[ing] harmful substances in products to which consumers are exposed, design[ing] standards to limit exposure to those substances, evaluat[ing] scientific studies supporting claims about the safety of products.”⁶¹ Congress found that “in connection with its mandate to promote health and reduce the risk of harm, the Food and Drug Administration routinely makes decisions about whether and how products may be marketed in the United States.”⁶²

Congress also made specific findings referencing the extensive findings of fact made by the United States District Court for the District of Columbia, including the finding that “the major United States cigarette companies have 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.”⁶³

These findings make it clear that the Tobacco Control Act is remedial legislation designed to address problems created by the conduct of the tobacco industry. The substantive authorities granted to the FDA should be read in this context.

Congress stated that a purpose of the Act was to provide FDA with authority to regulate tobacco products and recognized FDA as the primary federal regulatory authority with respect to the manufacture, marketing, and distribution of tobacco products.”⁶⁴ The Act authorized FDA “to set national standards controlling the manufacture of tobacco products and the identity,

⁵⁸

Id.

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Tobacco Control Act, Findings (2)-(3).

⁶⁰

Tobacco Control Act, Finding (29).

⁶¹

Tobacco Control Act, Finding (44).

⁶²

Id.

⁶³

Tobacco Control Act, Finding (49).

⁶⁴

Tobacco Control Act, Sec. 3(1).

public disclosure, and amount of ingredients used in such products.”⁶⁵ The Act also vested FDA “with the authority to regulate the levels of tar, nicotine, and other harmful components of tobacco products” and “to impose appropriate regulatory controls on the tobacco industry.”⁶⁶

The Act gave FDA numerous regulatory authorities and imposed numerous regulatory requirements on tobacco product manufacturers. Tobacco product manufacturers were required to provide FDA with a listing of “all ingredients. . . added by the manufacturer to the tobacco, paper, filter, or other part of each tobacco product by brand and by quantity. . . .” Sec. 904(a) The Act further required tobacco product manufacturers to provide FDA with a listing of all constituents, including smoke constituents as applicable, identified by the Secretary as harmful or potentially harmful to health in each tobacco product, and as applicable in the smoke of each tobacco product. . . .”⁶⁷ FDA was directed to establish and periodically revise a list of harmful and potentially harmful constituents, including smoke constituents, to health in each tobacco product by brand and by quantity.”⁶⁸

The Act also granted FDA regulatory authority to establish standards for tobacco products. Section 907 gives FDA authority, subject to certain limits, to establish standards applicable to all tobacco products.⁶⁹

C. The statutory standard for the granting of new product applications

The Tobacco Control Act subjected the marketing of new tobacco products to premarket review for the first time under a new and different regulatory standard designed specifically for application to the unique problems raised by tobacco products.⁷⁰ Under the Tobacco Control Act, no “new tobacco product” may be commercially marketed without the prior grant of an application by the FDA.⁷¹ A “new tobacco product” is any tobacco product that was not commercially marketed on February 15, 2007 and any modification of a product made

⁶⁵ Tobacco Control Act, Sec. 3(3).

⁶⁶ Tobacco Control Act, Sec. 3(5), (8).

⁶⁷ Tobacco Control Act, Sec. 904(a)(3).

⁶⁸ Tobacco Control Act, Sec. 904(e).

⁶⁹ A product standard established by FDA may require a reduction in nicotine content but may not, in the absence of Congressional action, require the abolition of nicotine.

⁷⁰ 21 U.S.C. 387j(a)(2). 21 U.S.C. 387j was designated as Section 910 in the bill as enacted and is referred as such in the text.

⁷¹ Id.

subsequent to that date.⁷² The statute directs FDA to deny an application to market a new product unless the manufacturer demonstrates that the marketing of the product is “appropriate for the protection of the public health.”⁷³ The statute directs FDA to make this determination “with respect to the risks and benefits to the population as a whole, including users and nonusers of tobacco products.” Moreover, the statute identifies, without limitation, two factors for FDA to include in its evaluation of the public health risks and benefits: (1) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and (2) the increased or decreased likelihood that those who do not use tobacco products will start using such products.⁷⁴ Under this standard, FDA must evaluate not only the effect of a product on those who use it, but also the likelihood that its presence in the market would cause nonusers of tobacco products to start or cause existing users not to quit. Even if a new product is no more toxic or addictive than any other product, if its presence in the market would increase the likelihood that nonusers would start or decrease the likelihood that existing users would quit, a decision to permit its marketing would not be “appropriate for the protection of the public health.” The requirements for the grant of a new product application are stringent and the amount of data an applicant must provide in support of an application is voluminous.⁷⁵

D. Tobacco products demonstrated to be substantially equivalent to a predicate product.

If a new tobacco product was commercially marketed subsequent to February 15, 2007 and before March 23, 2011, and the manufacturer filed an application within that time period to have the product deemed “substantially equivalent” to a product that was commercially marketed on February 15, 2007, the new product can continue to be commercially marketed indefinitely unless and until FDA denies the application.⁷⁶ Products for which substantial equivalence

⁷² 21 U.S.C. 387j (a)(1).

⁷³ 21 U.S.C. 387j (c)(2), (4). The Act also authorized FDA to issue product standards applicable to all tobacco products under substantially the same standard. 21 U.S.C. 387g.

⁷⁴ Id.

⁷⁵ See 21 USC 387j; FDA, Center for Tobacco Products, Draft Guidance for Industry: Applications for Premarket Review of New Tobacco Products,, Docket No. FDA-2011-D-0212 (2011), 76 Fed. Reg. 60,055 (Sept. 28, 2011).

⁷⁶ 21 U.S.C. 387j(a)(2)(B). The filing is to be made under 21 U.S.C. 387e(j) (subsection 905(j) of the bill). The filing under this subsection is designated as a “report.” As the purpose of the filing is to obtain a designation by FDA that the product is substantially equivalent to a predicate product, it functions as an application for such designation. For clarity, this paper will refer to a filing under section 905(j) as an application.

applications were filed after March 22, 2011 may not be commercially marketed unless and until FDA grants such an application.⁷⁷ The standards for consideration of such an application differ from those applicable to a new product application.⁷⁸ Once FDA has granted a substantial equivalence application, the product that was the subject of the application can itself become a predicate product for other applications. Accordingly, the FDA's decision to grant or deny a substantial equivalence application has greatly significant consequences.

Under the statute, a tobacco product is “substantially equivalent” to a predicate product if

“it has the same characteristics as the predicate product, or

“it has different characteristics and the information submitted [by the manufacturer] contains information, including clinical data if deemed necessary by the Secretary, that demonstrates that it is not appropriate to regulate the product under this section [i.e., the section requiring premarket approval for new products] because the product but does not raise different questions of public health.”⁷⁹

The statute defines “characteristics” as “the materials, ingredients, design, composition, heating source, or other features of a tobacco product.”⁸⁰

All products as to which substantial evidence applications are filed are, by definition, “new products.” The provisions of section 910 regarding “new products” apply unless they qualify for the exception created by section 905(j). As of August, 2012, tobacco product manufacturers had filed more than 3,500 substantial equivalence applications, but no tobacco product manufacturer had submitted a single new product application.⁸¹ In essence, tobacco product manufacturers are asserting that *none* of the more than 3,500 new tobacco products marketed or proposed to be marketed since February 15, 2007 has characteristics different from a

⁷⁷ 21 U.S.C. 387j(a)(2)(A).

⁷⁸ FDA, Center for Tobacco Products, Guidance for Industry and Food and Drug Administration Staff: Section 905(j) Reports: Demonstrating Substantial Equivalence for Tobacco Products, Docket No. FDA -2010-D-0635, 76 Fed. Reg.789(Jan. 6, 2011). Section 905(j) of the Tobacco Control Act is codified as 21 U.S.C. 387e(j). When FDA promulgated its guidance regarding the filing of reports under section 905(j), it stated that it was proceeding to do so without having first promulgated a draft guidance because of the imminence of the March 22, 2011 deadline imposed by statute.

⁷⁹ 21 U.S.C 387.j(a)(3)(A).

⁸⁰ 21 U.S.C. 387j(a)(3)(B). By definition, a product that has “the same characteristics” as the predicate product would not raise a different question of public health.

⁸¹ FDA, Center for Tobacco Products, response to Freedom of Information Act request of Dr. Gregory Connolly, June 14, 2012 (unpublished).

predicate product or raises “a different question of public health” from that raised by a predicate product marketed before that date.⁸²

The positions asserted by tobacco product manufacturers regarding substantial equivalence threaten to make the new product requirements of the Tobacco Control Act meaningless. If their positions are adopted, tobacco companies will continue to use the introduction of new and modified products just as they have done in the past—to addict, attract, and kill millions of Americans. Congress enacted the Tobacco Control Act to put a stop to these practices but unless FDA acts effectively to implement the statutory requirements the sections of the Act governing new or changed products will have no meaningful effect.

Most of the arguments asserted by the tobacco product manufacturers can be boiled down to the assertion that FDA’s interpretations of the substantial equivalence requirements would require them to change the way they have always done business, would make it far more inconvenient for them to market new products, and would in all likelihood reduce the number of new products that reach the market. All these things are true. However, any statute designed to protect the public health would require these results.

II. Legal standards for the consideration of substantial equivalence applications

A. The burden of proving each and every element of substantial equivalence is on the tobacco product manufacturer.

In our initial comments, the undersigned noted that the burden of meeting each and every criterion for products claimed to be substantially equivalent lies with the manufacturer.⁸³ In order to have an application for substantial equivalence granted, the tobacco product manufacturer is required by the statute to demonstrate that the characteristics of the new product are “the same” as that of the predicate product or, if they are not, that the new product does not

⁸² According to FDA officials, some of the 3,500 application cover more than one product. FDA Webinar of August 21, 2012. Thus, the number of products for which substantial equivalence designations is sought may be substantially greater than 3,500. Because FDA treats substantial equivalence applications as confidential, neither the number of products covered by such applications nor the identity of the new products for which such applications have been filed is public information.

⁸³ Initial comment filed in FDA-2010-D-0635 at 2 (Tab A) (March 22, 2011); comment filed in FDA-2011-D-0147 at 4 (Tab B) (March 8, 2011).

“raise different questions of public health.” None of the comments filed by tobacco product manufacturers explicitly challenges this formulation. However, the practical effect of the arguments they make is to reverse the burden of proof established by the statute and require FDA to grant a substantial equivalence application unless FDA demonstrates that the new product does *not* meet the criteria. This reversal of the burden of proof would not only contravene the statute but would effectively nullify the provisions of the statute relating to new products by creating an exception so broad that the general rule would have no application. The fact that there have been 3,500 applications for substantial equivalence and zero new product applications demonstrates that nullification of the new product standard is precisely what the industry seeks.

The statutory language unequivocally places the burden of proof on the manufacturer. FDA is directed to apply all the provisions of section 910 to any new tobacco product unless *the manufacturer “submits information that demonstrates that it is not appropriate”* to do so because the product does not raise different questions of public health. (emphasis added) It is not FDA’s burden to demonstrate that application of the new product requirements is appropriate; rather, the burden is on the manufacturer to demonstrate that application of the new product requirements is *not* appropriate. If the information submitted in the application is not sufficient to make this determination, then the Secretary must reject the application.

Had the drafters of the statute wished to place the burden on FDA to demonstrate the contrary they could have stated that a tobacco product that does not have the same characteristics as the predicate product would nevertheless be considered to be substantially equivalent to a predicate product *unless* FDA demonstrates that it raises different questions of public health. In fact, the comments of the tobacco product manufacturers urge FDA in essence to read the statute as if it had said this despite the fact that it says precisely the opposite.

The statutory language unequivocally places the burden of proof on the manufacturer. Indeed, the language in section 905(j) requiring tobacco products manufacturers to “report to the Secretary. . . the basis for such person’s determination that the tobacco product is substantially equivalent” to a predicate product, and precluding marketing absent an order finding substantial equivalence, is consistent with other parts of the FDCA that squarely place the burden on the product sponsor to satisfy the statutory standards. As the Supreme Court has recognized, the 1962 amendments to the FDCA shifted the burden squarely to the manufacturer to demonstrate

that its product was safe and effective for the intended conditions of use. *Wyeth v. Levine*, 129 S. Ct. 1187, 1195 (2009); *see also, e.g., General Medical Co. v. FDA*, 770 F.2d 214, 219 (D.C. Cir. 1985) (device manufacturer has burden in showing device meets reclassification standards). More specifically, in the context of substantial equivalence showings for medical devices – the provisions Congress used as a model when it drafted section 910 – a court has credited FDA’s conclusion that “the burden is always on the premarket notification submitter to demonstrate substantial equivalence. . . .” *Ethicon, Inc. v. FDA*, 762 F. Supp. 382, 391 (D.D.C. 1991) (internal quotation and FDA citation omitted) (emphasis added). Thus, the statement in the Guidance that a tobacco product manufacturer “must show” substantial equivalence is consistent with the plain language of sections 905(j) and 910(a)(3)(A) – and the post-1962 approach of the FDCA as a whole – placing the burden on the applicant to meet the statutory requirements.

Placement of the burden of proof is particularly important in contexts in which important information is unknown. If we knew all there was to know about the mechanisms by which tobacco products cause death and disease, resolving issues about substantial equivalence would be far easier. However, in a situation in which we know that using tobacco products causes death and disease and have identified many constituents as harmful, but cannot be certain we have identified every constituent that contributes to the harm caused by cigarettes, precisely what combination of constituents or the exact level of each constituent that cause death and disease or all of the mechanisms by which they do so, placement of the burden of proof is crucial. Given the current state of knowledge and the challenges of demonstrating to a certainty that a particular change in a tobacco product will increase the incidence of death and disease, the question is whether it is appropriate to permit the marketing of a new product that may increase the risk of death and disease without requiring the full range of premarket considerations mandated by section 910.

How certain does FDA have to be that permitting a new product to be marketed without applying section 910 will not increase the risk of death and disease in order to grant a substantial equivalence application? The statute provides a cautionary standard by which to answer that question. FDA is instructed not to grant an application unless the evidence submitted by the manufacturer demonstrates that the new product does not even “raise a different question” of public health. In other words, before it grants a substantial equivalence application, FDA must

be satisfied that there is no plausible reason to believe that the new product is any more likely to increase the risk of death and disease than the predicate product.

A useful way to consider the issue is to ask what the consequence of FDA's making an erroneous decision would be. The consequence of erroneously denying a substantial equivalence application would be to require a manufacturer to meet the standards of section 910 before it could market the new product. Such a result would make it more difficult for tobacco product manufacturers to introduce new products that cause death and disease. Conceivably, tobacco product manufacturers might be prevented from selling some products that might turn out to be no more lethal or addictive or appealing to youth than existing products. If, however, a substantial equivalence application were erroneously granted and the product turned out to increase the risk of death and disease, then more people would likely die prematurely from tobacco-related death and disease as the result of an erroneous decision. It is evident that the potential harm created by erroneously granting a substantial equivalence application outweighs the potential harm created by erroneously denying such an application. Given the disproportionate impact of these alternative results, Congress was wise to place the burden of proof on the manufacturer to justify why such a product should be marketed without having met the requirements of section 910.

The principal strategy the tobacco product manufacturers employ to reverse this key presumption is very similar to the strategy that they used for so many decades to argue that cigarettes had not been shown to cause cancer: the argument that because they claim science cannot specify precisely how a given variable causes disease, regulatory policy should proceed on the assumption that no connection exists. Thus, for example, in the face of evidence that ammonia intensifies the addictive effect of nicotine, the manufacturers argue that it has not been conclusively demonstrated that such an effect prevails.⁸⁴ In the face of evidence that burning sugar produces acetaldehyde and other aldehydes and that such substances intensify the addictive effect of nicotine, the manufacturers argue that it has not been conclusively demonstrated that such an effect prevails.⁸⁵ In fact, in the face of evidence that numerous additives alter the

⁸⁴ Comments of Philip Morris, USA, Inc. and US Smokeless LLC in FDA-2010-N-646 at 4-5 (March 22, 2011); Comments of R.J. Reynolds Tobacco Corp. in FDA-2010-N-0646 at 10 (March 21, 2011).

⁸⁵ Comments of Philip Morris, USA, Inc. and US Smokeless LLC in FDA-2010-N-646 at 4-5 (March 22, 2011).

pharmacological effect of nicotine in the brain, the manufacturers argue that there is no conclusive evidence of such an effect.⁸⁶ It may well be that in some of these instances the science available currently to the FDA demonstrating a cause and effect relationship between an increased level of an additive and an increase in addiction remains uncertain. However, the absence of such evidence provides no basis for implementing regulatory authority on the supposition that no such relationship exists. The burden of proof is not on FDA to demonstrate that increased levels of an additive cause specific results; rather, where for example, there is a basis for believing that increasing the level of an additive might increase the abuse potential of the product, the burden of proof is on the manufacturer to demonstrate the absence of any such increase. Manufacturers should no longer be permitted to use the public as experimental guinea pigs. No product should be found substantially equivalent to a predicate product unless the manufacturer has satisfied its burden.

There can be no doubt that the tobacco product manufacturers intend by their arguments to prevail by reversing the burden of proof. They make their arguments not merely with regard to specific additives, but with regard to anything that can be done to change a cigarette. The fundamental argument made by the tobacco product manufacturers is that all cigarettes are lethal and that therefore changing anything about the product does not increase the risk to public health. This argument is a monstrous fallacy. Substantial evidence exists that there are many changes in cigarettes that increase the risk to public health. Such changes can come about because of changes in the type of tobacco in the rod, the identity and the level of additives, or changes in product design, such as changes in the size of the product, the filter, paper, or ventilation. Even if the level of harmful or potentially harmful constituents does not vary in machine testing, changes that alter smoking topography—the way a smoker actually uses the product, such as the intensity of puffing or the number of puffs per cigarette—can affect the disease risk presented by the product.

The fundamental question at the heart of the debate about standards for substantial equivalence is who bears the burden of proof that changes in the status quo may be harmful to the public health before the industry is prevented from making such changes. Before enactment

⁸⁶ e.g., Comments of Philip Morris, USA, Inc. and US Smokeless LLC in FDA-2010-N-646 at 5 (March 22, 2011).

of the Tobacco Control Act, this question was not even asked. The industry was free to make whatever changes in tobacco products it wished. It made changes with the sole aim of maximizing the manufacturers' profit without regard to consequences for the public health. The result has been that cigarettes became the largest preventable cause of death in the United States. Unregulated innovation in cigarette design and content has not made cigarettes less lethal, but has made them more addictive, more attractive, and may have made them more lethal. The Tobacco Control Act gives FDA authority to change this outcome by preventing product changes unless it can be shown that such changes "do not raise different questions of public health." Because the tobacco product manufacturers created the public health crisis that gave rise to the Tobacco Control Act, it is altogether appropriate to place the burden on them to establish that the product changes they propose to make "do not raise different questions of public health."

Tobacco product manufacturers complain that application of the statutory standard in the manner proposed by FDA would require them to make substantial changes in the way they bring products to market. There is no question that it would do precisely that. However, that result is intentional because the purpose of the Tobacco Control Act was not to perpetuate a status quo that is universally recognized as unacceptable, but rather to require substantial changes. The changes required by the statute could result in fewer new tobacco products being brought to market. However, a century's experience has conclusively demonstrated that such product changes have led to a public health disaster. The fact that "this is the way the industry has always done things" is not a persuasive argument for continuing such practices; if anything, it is an argument for changing them. Changing the results requires changing the rules, and Congress has done just that.

The arguments of the tobacco product manufacturers are particularly unpersuasive in light of the fact that the reason so little is known about the precise health effects of product changes is that until the enactment of the Tobacco Control Act tobacco companies refused to divulge the contents of their products, avoided doing the research that might have advanced the state of our knowledge, and suppressed or misrepresented the results of that research that was done. Having prevented by their own conduct the development of a more complete understanding of the consequences of product changes, the tobacco product manufacturers now

demand the right to continue altering their products unless there is conclusive evidence that the alterations will increase death and disease. The audacity of this argument is remarkable.

B. The statutory standard that characteristics of a new product be “the same” as the characteristics of the predicate product has a quantitative as well as a qualitative dimension and the words of the statute should be given their literal meaning.

In their comments on the FDA’s proposed guidance, tobacco product manufacturers have argued that the term “the same characteristics” should not require the characteristics of the new product to be identical to the characteristics of the predicate product. They argue that a product that is “identical” to a new product is neither new nor modified and that requiring the characteristics to be identical would render the definition meaningless.⁸⁷ Moreover, they maintain that alteration of ingredients in conventional tobacco products “do not substantially alter smoke toxicity” and hence that such products all have “the same characteristics.”⁸⁸

Public health advocates argue that both the language of the statute and its purpose require that the content be identical, or at least nearly identical for it to be considered to have the same characteristics of the predicate product.⁸⁹ Moreover, they dispute the allegation that such a reading would render the definition meaningless.⁹⁰ They also dispute the assertion that the ingredients typically used in modern cigarettes do not substantially alter smoke toxicity and assert that even if this allegation were valid alterations in ingredients can and do affect the addictiveness of the product and the risks and benefits to the population as a whole.⁹¹

The statute requires that the characteristics of the product be shown to be “the same” as those of the predicate product in order to qualify for substantial equivalence.⁹² The lack of a

⁸⁷ Comments of Philip Morris USA Inc. and U.S. Smokeless Tobacco Company LLC in Docket No. FDA-2010-D-0635 at 5-6 (Feb. 8, 2011); Comments of Lorillard Inc. in Docket No. FDA-2010-D-0635 at 2-3 (Feb. 4, 2011).

⁸⁸ Id.

⁸⁹ See comments of American Cancer Society Cancer Action Network, *et.al.*, in Docket No. FDA-2010-D-0635 at 3-4 (March 22, 2011); comments of American Cancer Society Cancer Action Network, *et al.*, in Docket No. FDA-2011-D-147 at 13-14 (Nov. 8, 2011).

⁹⁰ See comments of American Cancer Society Cancer Action Network, *et.al.*, in Docket No. FDA-2010-D-0635 at 4-7 (March 22, 2011).

⁹¹ Id.

⁹² A new tobacco product that does not have “the same characteristics” as the predicate product can still qualify as substantially equivalent if it does not raise different questions of public health.

qualifying adjective in the statutory language suggests that each element of the product must be identical to the predicate product. The requirement that characteristics be “the same” has both a qualitative and a quantitative dimension: i.e., the characteristics must be the same and they must be present in the same quantity. The presence of additives or other substances in the product that are not present in the predicate product would mean that the product did not have “the same” characteristics as the predicate product. Moreover, even if there is qualitative identity, quantitative differences in the level of any substance would also mean that the product did not have “the same” characteristics. Despite the statutory language, it might be reasonable to allow for a level of quantitative variance based on the proven sensitivity of measurement; however, no variance in excess of such a level ought to be permitted, nor should such a variance be allowed until standards have been established by the FDA.

Contrary to the arguments made by the tobacco product manufacturers, the requirement that characteristics be “the same” does not render the standard meaningless.⁹³ A product that is physically the same as a predicate product may be rebranded with a new name. As the FDA has noted, offering the product with a new name renders it a new product, but the same physical characteristics would mean that it would qualify for review as “substantially equivalent” taking into account the impact of its name change, new packaging and marketing in terms of appeal to non-tobacco users. Moreover, for these purposes, requiring that physical characteristics be “the same” is not unreasonably rigid because there exists an alternative standard by which a product that is deemed not to have “the same characteristics” can still be found to be “substantially equivalent” (i.e., it is substantially equivalent if it “does not raise different questions of public health”).

C. The “same characteristics” analysis must include smoke constituents.

Some major tobacco product manufacturers have argued that smoke constituents should not be considered “other features” of a tobacco product for purposes of determining substantial equivalence. If this argument were accepted, FDA would be foreclosed from comparing the level of toxic or addictive substances in the smoke of a combusted new tobacco product with the level

⁹³ See, e.g., Comments of Philip Morris USA Inc. and U.S. Smokeless Tobacco Company LLC in Docket No. FDA-2010-D-0635 at 5-6 (Feb. 8, 2011); Comments of Lorillard Inc. in Docket No. FDA-2010-D-0635 at 2-3 (Feb. 4, 2011).

of toxic or addictive substances in the smoke of the predicate product in evaluating a substantial equivalence application. The principal purpose of the statute is to institute a regulatory regime to protect the public health. Because the presence of toxic or addictive constituents in the smoke of a tobacco product is a central—if not the most important—determinant of how harmful the product is to the public health, failure to consider the relative levels of toxic or addictive substances in the smoke of the two products would frustrate the essential purpose of the statute. There is no principled reason to conclude that the level of toxicants in an unburned cigarette should be relevant while the level of toxicants in its smoke is not. Such a suggestion is comparable to suggesting that the Environmental Protection Agency could effectively protect the public from ambient air pollution by regulating the level of potential pollutants in unburned fuel but ignoring the level of pollutants emitted into the atmosphere.

Philip Morris contends that a level of toxic or addictive substances in a subject product that is higher than that in the predicate product should not preclude a product from being deemed substantially equivalent because variations in the content of such substances may not render such products any more dangerous than the predicate product and because constituent data for most predicate products are unavailable.⁹⁴

As noted above, tobacco product manufacturers have argued that changes in the level of individual toxicants and other additives do not change the overall toxicity of combustible tobacco products and that therefore it is inappropriate to consider the quantitative increases in the level of individual toxicants or other substances in determining substantial equivalence. This argument is scientifically unsupportable and, if accepted, would reverse the statutory allocation of the burden of proving substantial equivalence.

First of all, it is by no means clear that changes in the level of individual toxicants or groups of toxicants or other additives do not increase the toxicity or addictiveness of the tobacco product. For example, the World Health Organization Study Group on Tobacco Product Regulation (TobReg) concluded that “acetaldehyde. . .is a known carcinogen that appears to potentiate the dependence-causing effects of nicotine. Chocolate and its derivatives are added to indirectly facilitate the development of dependence by contributing flavor. . .and this appears to

⁹⁴ Comments of Philip Morris USA Inc. and U.S. Smokeless Tobacco Company LLC in Docket No. FDA-2010-D-0635 at 7-8 (Feb. 8, 2011).

increase the carcinogenicity of smoke.”⁹⁵ The Study Group concluded that “from a public health standpoint it is difficult to justify allowing very high levels of carcinogens in some cigarette brands when other brands have only a fraction of those levels, even if there is uncertainty about the magnitude of the benefit of reducing a single constituent.”⁹⁶

The argument made by tobacco product manufacturers confuses the inability to specify precisely which substances (and in what combination) make some tobacco products more lethal than others and to quantify the degree of difference with proof that the level of such substances is immaterial to public health. In essence, this argument would put the burden of showing precisely how individual toxicants cause disease on FDA. The industry seeks to continue to market new tobacco products regardless of the level of toxicants without regulatory constraint unless FDA can demonstrate precisely how such toxicants cause disease. Similarly, the industry seeks the same exemption with regard to the level of addictive substances and other substances that exacerbate the addictive potential of the product. These assertions are contrary to the provisions of the statute. Section 910 directs the Secretary to deny any new product application *unless the applicant demonstrates* that its marketing would be appropriate for the protection of the public health. The burden of establishing that it would be inappropriate to apply the new product standards pursuant to a substantial equivalence application is similarly on the applicant.

D. Increases in the likelihood of initiation by nonusers and decreases in the likelihood of cessation by existing users are “questions of public health” as that term is used in the definition of “substantial equivalence” under Section 910.

The statute makes it clear that the question of whether the granting of a new product application is “appropriate for the protection of public health” requires a determination with respect to the risks and benefits to the population as a whole (both smokers and nonsmokers) and includes an evaluation of whether granting the application would increase or decrease the likelihood that nonusers would start using tobacco products or that existing users would quit.

⁹⁵ World Health Organization, Study Group on Tobacco Product Regulation, *The Scientific Basis of Tobacco Product Regulation* at 11 (2007). This report cites numerous other examples where changes in the level of toxic or non-toxic substances in product design or in smoke constituents can alter the toxicity or addiction potential of the product.

⁹⁶ *Id.* at 102.

Applying a standard that considers the effect of regulatory action on “the public health” is fundamentally different from applying a standard that considers only whether a product is more or less toxic or addictive to an individual user.

Products that were marketed on February 15, 2007 are permitted to remain on the market in the absence of the promulgation of a tobacco product standard under section 907. Since the fundamental purpose of the statute is the protection of the public health, products that “do not raise different questions of public health” (i.e., questions of public health different from those raised by an existing product) are also permitted to remain on the market. In making substantial equivalence determinations, FDA must establish criteria for determining when products with different characteristics from the predicate product “do not raise different questions of public health.” The essential question FDA must address is how “public health” should be defined. If a new product is found not to be “substantially equivalent” to a predicate product, the consequence is that it cannot be marketed unless FDA grants a new product application under section 910(c). The statute directs FDA to deny any new product application unless the applicant demonstrates that the marketing of the new product would be “appropriate for the protection of the public health.” The statute sets forth the questions FDA must consider in making this determination. Thus, section 910(c) itself specifies the elements that constitute “a question of public health.”

Section 910(a)(3)(ii), which defines substantial equivalence, and Section 910(c), which establishes the standard for consideration of a new product application, are closely related. Both standards are concerned with the protection of the public health. Indeed, the purpose of the substantial equivalence determination is to establish a category of new products for which it is unnecessary to require a new product application because it would be reasonable to conclude on the basis of the evidence provided that such products would cause no more harm to the public health than an existing product. Thus, it is reasonable to conclude that “public health” as it is used in the definition of substantial equivalence (section 910(a)(3)(ii)) should be given the same meaning as the term “public health” as it is used in section 910(c). Therefore, in determining whether a new product that does not have the same characteristics as the predicate product “raises a different question of public health,” the relevant inquiry should not be restricted to the effect of the product on the disease risk of an individual user, but should also include the effect of the marketing of the product on the population as a whole. A new product that is more likely

to cause an increase in use by non-users than the predicate product “raises a different question of public health;” a new product that is more likely than the predicate product to cause a decrease in cessation by existing users also “raises a different question of public health.” Had the drafters of the statute intended to restrict the scope of substantial equivalence inquiries to those involving the disease risk of the product to individual users, they would not have used a term (i.e., “public health”) to which they gave a much broader meaning elsewhere in the same section. It would not be reasonable to conclude that Congress was indifferent to the effect of any new product on the general population and thus it would not be reasonable to exclude such effects from consideration in the evaluation of a substantial equivalence application. The purpose of the substantial equivalence exception was to permit the marketing of a product only where the manufacturer could demonstrate that the product would have no more harmful effect on the general population than the predicate product. Unless a product has “the same characteristics” as the predicate product, consumer perception of the product—and likely consumer behavior in response to its marketing-- is a necessary consideration in determining substantial equivalence.

Application of this analysis still recognizes an important distinction between substantial equivalence filings and new product applications. For purposes of a substantial equivalence filing, analysis of the public health impact compares the effect on the public health of the new product only to that of the predicate product. By contrast, if the product were the subject of a new product application, the public health effects of the new product would be analyzed with reference to the market as a whole. Thus, some products found substantially equivalent to a predicate product might not meet the standards for the grant of a new product application.

Tobacco product manufacturers take the position that “Congress excluded any consideration of behavioral effects from the substantial equivalence criteria.”⁹⁷ They also take the position that “reduction or elimination of an additive should be categorically exempt from substantial equivalence requirements,”⁹⁸ that substantial equivalence reports should not even

⁹⁷ Comments of Philip Morris USA and U.S. Smokeless Tobacco Company, LLC in Docket No. FDA-2010-N-0646 at 4 (March 22, 2011).

⁹⁸ *Id.* at 6-7.

require reporting on harmful or potentially harmful constituents,⁹⁹ and that modifications in tobacco blends or adjustments in cigarette ventilation should also be categorically exempted.¹⁰⁰

Tobacco product manufacturers essentially take the position that because products marketed on February 15, 2007 cause death and disease, new products that also cause death and disease do not raise different questions of public health. Such a definition of what constitutes “different questions of public health” is so restrictive that it would have no practical relevance. And that is precisely how tobacco product manufacturers have interpreted it. As previously noted, more than 3,500 substantial equivalence requests have been filed but there has been not a single new product application. According to the industry, every single tobacco product marketed or proposed to be marketed since February 15, 2007 is substantially equivalent to a product marketed on that date. As interpreted by the tobacco companies, the exception is so broad that it swallows the general rule. If the FDA adopts the industry’s interpretation of substantial equivalence, the new product provisions of the statute would have been rendered meaningless. More important, the protections for the public health envisioned to result from the statute would not have been achieved.

E. Tobacco product manufacturers must demonstrate that modifications to a tobacco product are not likely to increase initiation of tobacco use, particularly by youth, even where the modification increases neither the toxicity nor the addiction potential of the product.

Philip Morris urges FDA to adopt a standard for substantial equivalence that focuses exclusively on changes in toxicity.¹⁰¹ Such a policy, however, would be consistent with neither the statutory language nor the statutory intent. FDA is directed to consider product changes that impact the public health, whether such changes do so by changing toxicity, addictiveness, or the likelihood that a product will increase youth initiation. A policy that ignores either addictiveness or youth initiation would not protect public health.

⁹⁹ Comments of Philip Morris, USA Inc. and U.S. Smokeless Tobacco Company in Docket No. FDA-2011-D-0147 at 12-13 (November 8, 2011).

¹⁰⁰ *Id.* at 7.

¹⁰¹ Comments of Philip Morris USA Inc. and U.S. Smokeless Tobacco Company LLC in Docket No. FDA-2010-D-0635 at 6-8 (Feb. 8, 2011).

Philip Morris's argument would exclude even products as to which the changes increased the abuse liability of the product. As demonstrated above, numerous modifications to tobacco products have this effect.¹⁰² It is apparent that any standard that excluded consideration of abuse liability in the determination of substantial equivalence would be wholly inconsistent with the statute.

In addition, however, modifications in a product that increase neither the toxicity nor the abuse liability of the product should also be considered in determining whether a new tobacco product is substantially equivalent to a predicate product. As demonstrated above, product modifications have been used extensively either to impart a flavor, mask a taste, or otherwise affect the smoker's sensory experience in ways that increase the number of new users or decrease the likelihood of quitting. (See discussion at 21-25, *supra*).

Philip Morris argues that it is too hard to measure a tobacco product's propensity to increase initiation and therefore that no meaningful standard could be established.¹⁰³ However, tobacco product manufacturers have spent hundreds of millions of dollars conducting market acceptance tests to measure the effect of product changes on potential consumers, including measuring the relationship between product design and initiation.¹⁰⁴ The assiduous attention paid to such consumer acceptance studies by tobacco companies is demonstrated by vast numbers of internal documents intensely analyzing such effects. The industry's efforts to design products to appeal to specific segments of the market are enormous and their ability to measure the relationship between product design and addiction is extremely high. In its report on menthol, the Tobacco Products Scientific Advisory Committee described the companies' efforts as follows:

The planning of promotional strategy requires the definition of a clear market, whereby population is segmented into defined subgroups. This target market can include people who are potential buyers, current users, those who make the buying decision, or those who influence it. Extensive qualitative and quantitative research is undertaken to identify

¹⁰² U.S. v. Philip Morris, 449 F. Supp. 2d 1, 309-315; TobReg (2012) at 16; Rabinoff M, Caskey N, Rissling A, and Park C, Pharmacological and Chemical Effects of Cigarette Additives, 97:11 American Journal of Public Health, pp. 1981-1991, November 2007.

¹⁰³ Comments of Philip Morris, USA, Inc. and US Smokeless LLC in FDA-2010-N-0646 at 5 (March 22, 2011).

¹⁰⁴ See, e.g., U.S. v. Philip Morris, *supra*, 449 F. Supp. 2d 1, 691-92.

the salient beliefs, values and preferences of the planned target market, which might be defined on the basis of age, gender, ethnicity, income and lifestyle, among other attributes. Promotional strategies are then designed for and directed to this well-defined consumer group (or segment). The message in a segmented campaign may have broad appeal, but will be most salient to and resonate with the specific targeted segment.¹⁰⁵

Tobacco companies have demonstrated by their conduct that measuring a product's propensity to induce initiation is something they consider and test so that it is critical that FDA also take these factors into account. The TPSAC Report on menthol provides a model for how FDA can do so.

Moreover, Philip Morris disclaims any knowledge of or ability to measure addictiveness or appeal to, or use by minors.¹⁰⁶ However, the facts demonstrate otherwise. The U.S. District Court for the District of Columbia made voluminous findings demonstrating the deliberate, sustained and successful efforts of all the major tobacco companies to market their products to underage users.

The evidence is clear and convincing—and beyond any reasonable doubt—that Defendants have marketed to young people twenty-one and under while consistently, publicly, and falsely, denying they do so. . . Defendants intensively researched and tracked young people's attitudes, preferences, and habits. . . Defendants used their knowledge of young people to create highly sophisticated and appealing marketing campaigns targeted to lure them into starting smoking and later becoming nicotine addicts. . . Defendants spent billions of dollars every year on their marketing activities in order to encourage young people to try and then continue purchasing their cigarette products in order to provide the replacement smokers they need to survive.

449 F. Supp. 2d at 691-92.

Philip Morris's false and self-righteous disclaimer of knowledge about the appeal of the company's products to youth contrasts with its own internal documents. In one typical internal memorandum, a Philip Morris executive stated,

[I]t is important to know as much as possible about teenage smoking patterns and attitudes. Today's teenager is tomorrow's regular customer, and the overwhelming

¹⁰⁵ TPSAC menthol report, *supra*, note 15 at 68.

¹⁰⁶ Comments of Philip Morris, USA, Inc. and US Smokeless LLC in FDA-2010-N-646 at 5 (March 22, 2011).

number of smokers first begin to smoke when they are still in their teens.... The smoking patterns of teenagers are particularly important to Philip Morris.¹⁰⁷

As noted above, the TPSAC, after exhaustive review of the available data, concluded that the use of menthol as a characterizing flavor—at carefully calibrated levels—had the effect of promoting the initiation of tobacco use among adolescents. Use of menthol at higher levels renders the smoke harsh and irritating and unacceptable to inexperienced smokers. Use of menthol at lower levels hits the sweet spot for adolescents. The developers of Newport and Marlboro Menthol were not just lucky: their hard work monitoring the preferences of America’s youth was rewarded.

In evaluating a proposed change in the level of an additive or any other change in product design for which a substantial equivalence application is made, FDA should require production of all consumer acceptance and other marketing studies conducted by the company and all other documents relating to the company’s analysis of how the product is expected to perform in the market, what market it is being targeted to, and why the company believes the new or modified product should be introduced. Such studies are directly relevant to the statutory standard. FDA must have access to these studies to fulfill its statutory responsibility. If the industry claims no such studies exist, FDA should require that they be done just as they do for any drug with abuse potential.

Analytically, however, FDA may recognize a distinction between substances that neither increase the toxicity or the abuse liability of the product or substances that do so. An increase in the level of a component or smoke constituent that increases toxicity or addiction potential compared to the predicate product would require the denial of an application for substantial equivalence. However, depending on the content of consumer acceptance studies, a change in the level of a component or smoke constituent that affects neither toxicity nor abuse liability, would not necessarily prevent a product from being found to be substantially equivalent to a predicate product if FDA concluded that adequate evidence has been presented that it would not increase initiation or decrease cessation.

¹⁰⁷ Memorandum from Myron Johnston of Philip Morris Bates No. 1000390808 (1981), quoted in National Cancer Institute Monograph 19 at 57.

F. Congress did not intend the regulatory requirements for establishing substantial equivalence for tobacco products to be the same as the regulatory requirements for establishing substantial equivalence for medical devices.

Several tobacco product manufacturers argue that the regulatory requirements for establishing substantial equivalence for tobacco products should be the same as the requirements for establishing substantial equivalence for medical devices.¹⁰⁸ This argument is wrong. Neither the statutory language, the legislative history, nor the fundamental purposes of the regulatory scheme support this argument.

1. The statutory language of the two sections is not the same.

The starting place for statutory construction is with the language of the statute itself.. *Jimenez v. Quarterman*, 129 S.Ct. 681, 685 (2009) (citations omitted). Comments filed by Liggett contend that because both the device and tobacco provisions use the term “substantial equivalence,” they must mean the same thing.¹⁰⁹ That contention is incorrect. In the FDCA, Congress wrote different definitions for the term in two sections of the FDCA. In the medical device provisions of Chapter V of the FDCA, Congress defined “substantial equivalence” as follows:

(i) Substantial equivalence

(1) (A) For purposes of determinations of substantial equivalence under subsection (f) of this section and section 360j (l) of this title, the term “substantially equivalent” or “substantial equivalence” means, with respect to a device being compared to a predicate device, that the device has the same intended use as the predicate device and that the Secretary by order has found that the device—

(i) has the same technological characteristics as the predicate device, or

(ii) (I) has different technological characteristics and the information submitted that the device is substantially equivalent to the predicate device contains information, including appropriate clinical or scientific data if deemed

¹⁰⁸ Comments of Liggett Group LLC in FDA-2010-D-0635 at 3-6 (June 10, 2011); Comments of Commonwealth Brands, Inc., et al., in FDA-2010-D-0635 and at 8-11 (March 3, 2011).

¹⁰⁹ Comments of Liggett Group LLC in FDA-2010-D-0635 at 3-6 (June 10, 2011).

necessary by the Secretary or a person accredited under section 360m of this title, that demonstrates that the device is as safe and effective as a legally marketed device, and

(II) does not raise different questions of safety and effectiveness than the predicate device.

(B) For purposes of subparagraph (A), the term “different technological characteristics” means, with respect to a device being compared to a predicate device, that there is a significant change in the materials, design, energy source, or other features of the device from those of the predicate device.

FDCA § 513(i).

In Chapter IX of the FDCA, Congress defined the term in the context of tobacco products as follows:

(3) Substantially equivalent defined

(A) In general

In this section and section 905(j) of this title, the term “substantially equivalent” or “substantial equivalence” means, with respect to the tobacco product being compared to the predicate tobacco product, that the Secretary by order has found that the tobacco product—

(i) has the same characteristics as the predicate tobacco product; or

(ii) has different characteristics and the information submitted contains information, including clinical data if deemed necessary by the Secretary, that demonstrates that it is not appropriate to regulate the product under this section because the product does not raise different questions of public health.

(B) Characteristics. In subparagraph (A), the term ‘characteristics’ means the materials, ingredients, design, composition, heating source, or other features of a tobacco product.

FDCA § 910(a)(3).¹¹⁰

¹¹⁰ The FDCA states, in the definition of “tobacco product,” that the term “does not mean an article that is . . . a device [as device is defined in FDCA § 201(h)].” FDCA § 201(rr).

The differences in the two definitions are significant. First, as noted above, if a new tobacco product has different characteristics from the predicate product, FDA must determine whether the data submitted by the tobacco product sponsor “raise[s] different questions of public health.” By contrast, the device definition requires FDA to determine whether the data supporting a device with “different technical characteristics” demonstrate that the product is “as safe and effective as the predicate device” and does not raise different questions of safety and effectiveness from those raised by the predicate device. Congress established the “public health” standard for tobacco because it recognized that predicate tobacco products have never been, and could not be, demonstrated to be “safe,” nor have they been scientifically examined by any federal agency. In 2000, when the Supreme Court ruled that the existing Food, Drug and Cosmetic Act did not give FDA jurisdiction to regulate tobacco products, it concluded that the existing regulatory standards applicable to food, drugs, and medical devices could not appropriately be applied to tobacco products and it reasoned that Congress therefore could not have contemplated the regulation of tobacco under such standards.¹¹¹

The difference in the two statutory schemes is fundamental. For devices, the predicate products are “safe” and their safety has previously been studied by the FDA. For tobacco products, the predicate products are not “safe” and they have never been subject to government oversight. For medical devices, the predicate products are “effective,” meaning they actually help users; for tobacco products the concept of effectiveness has no relevance. Congress recognized that medical devices have substantial social value: they help treat and prevent disease and contribute to the protection of the public health. There is a strong argument for encouraging innovation in medical devices. Tobacco products are not safe. In fact, the entire regulatory scheme is designed to protect the public from their dangers.

Congress sought to achieve an affirmative public health goal when it adopted the public health standard for tobacco products. As stated in a 2008 House report on H.R. 1108, a predecessor to the Tobacco Control Act, “[t]he public health standard is intended to be a flexible standard that focuses on the overall goal of reducing the number of individuals who die or are harmed by tobacco products.” H.R. Rep. 110-762, at 78 (2008).

¹¹¹ Brown & Williamson Tobacco Corp. v. FDA, 529 U.S. 120, 137 (2000).

A second difference in the definitions is that, in section 513(i), Congress defined “different technological characteristics” to mean a “*significant* change” in the devices materials compared to the predicate device. In section 910, by contrast, Congress did not require that the differences in the “characteristics” of the new tobacco product be “significant” to trigger the substantial equivalence assessment. This change in the definition for tobacco also makes sense. In the context of medical devices, Congress had a measure of confidence that a device that differs only in minor respects from the predicate device is likely to be similarly safe and effective as the prior approved product. In the tobacco context, however, Congress was justifiably concerned that even minor changes to a tobacco product could raise different public health questions compared to the predicate, which itself never was subjected to any scientific or regulatory scrutiny. Thus, Congress excluded the “de minimis” differences allowance for new tobacco products that are the subject of substantial equivalence reports.

The canon of statutory construction that Liggett suggests must govern – “identical words appearing more than once within a statute are presumed to have the same meaning” (Liggett comments at 4) – is inapplicable here. First, as described above, the phrases do *not* have the same meaning – Congress expressly changed the definition in Chapter 9 of the FDCA to tailor it to be appropriate for regulating tobacco products.¹¹² Here, Congress’s inclusion of an entirely separate definition in section 910 provides “strong textual support” for the conclusion that Congress intended the term “substantial equivalence” to mean something different in the tobacco chapter of the FDCA. *See Gustafson v. Alloyd Co.*, 513 U.S. 561, 573 (1995).¹¹³

¹¹² Liggett’s quotation from *Morrisette v. United States*, 342 U.S. 246 (1952), thus supports FDA’s interpretation of section 910 in the Guidance. In that case, the Supreme Court stated that terms should be given their established meaning unless there is “contrary direction.” Here, Congress’s inclusion of a tobacco-specific definition of “substantial equivalence” is exactly the “contrary direction” that Congress intends the term to have a different meaning in the context of tobacco products.

¹¹³ For the reasons discussed herein and recognized by Congress in the drafting of those provisions, it would have been nonsensical and impossible in the drafting of the tobacco chapter of the FDCA to incorporate the definition from the device provisions into the tobacco provisions without amendment, or to interpret them in the same way. *Cf. Robinson v. Shell Oil*, 519 U.S. 337, 343 (1997) (recognizing that a statutory term “may have a plain meaning in the context of a particular section—not that the term has the same meaning in all other sections and in all other contexts” and that there are circumstances where “each section must be analyzed to determine whether the context gives the term a further meaning...”); *Estate of Cowart v. Nicklos Drilling Co., et al.*, 505 U.S. 469, 501 (Blackmun, J., dissenting) (“It is not unusual for the same word to be used with different meanings in the same act, and there is no rule of statutory construction which precludes the courts from giving to the word the meaning which the legislature intended it should have in each instance.”) (quoting *Atlantic Cleaners & Dyers, Inc. v. United States*, 286 U. S. 427, 433 (1932)).

2. The Legislative History Confirms That Congress Recognized That Differences Between Devices and Tobacco Products Required Different Regulatory Approaches and Gave FDA Discretion in Enforcing the Tobacco Provisions.

Contrary to Liggett’s statements about congressional intent, the legislative history confirms that Congress intentionally defined “substantial equivalence” terms differently in the Tobacco Control Act because it recognized that the “safety and effectiveness” standard that governs FDA regulation of medical devices does not and cannot apply in the context of tobacco products, which are not intended to treat any disease or condition and which, when used as intended, cause disease. Consistent with that recognition, and consistent with the 2008 House Report that the “public health” standard was intended to be “flexible,” the 1998 Senate report to S. 1415 (the so-called “McCain” tobacco bill that set out in significant respects the framework for the Tobacco Control Act) stated that Congress authorized, but did not require, FDA to interpret the tobacco provisions that were similar to device provisions in the same way as it interpreted those device provisions: “The bill creates a separate chapter for tobacco products, and thus, *expressly directs the Secretary to maintain a distinct regulatory program for tobacco products*. However, the Secretary *may* follow precedents involving, decisions under, and interpretations of, comparable provisions governing devices under Chapter V *to the extent the Secretary deems appropriate* for tobacco products. S. Rep. No. 105-180, at 16 (emphasis added). Such statements reflect Congress’s intent from the earliest iterations of what became the Tobacco Control Act to give FDA considerable leeway in enforcing the “public health” standard. FDA’s decision in the Guidance to read the substantial equivalence definition to require comparison to a single predicate product – an interpretation coming straight from the plain language of the statute – represents precisely the sort of judgment entrusted to FDA by Congress.

The legislative history also shows that Congress created an entirely separate chapter of the FDCA for tobacco products because it recognized that a different statutory regime was necessary in light of the fundamental distinctions between tobacco products and drugs or medical devices. In summarizing S. 1415, the Senate Report acknowledged the important distinction

between the “public health” and “safety and effectiveness” ultimately reflected in the different definitions of “substantial equivalence” in sections 513 and 910:

Tobacco products raise different public health issues than medical devices regulated under Chapter V of the Federal Food, Drug, and Cosmetic Act (FDCA). While maintaining to the greatest extent practical the full range of authorities that the Secretary and FDA would have exercised over these products as devices, the bill modifies and adapts certain FDCA device authorities so that they are more appropriate to address the unique problems encountered in regulating tobacco products. Therefore, the Committee believes that it is appropriate to create a separate chapter of the FDCA....

....Some of the medical device authorities have, however, been modified to reflect the special concerns raised by the regulation of tobacco products. For example, in regulating devices under Chapter V, the Secretary must determine whether the regulatory actions taken will “provide reasonable assurance of the safety and effectiveness” of the device. Under the provisions of Chapter IX, this standard has been replaced with the requirement, to be used only for tobacco products, that the Secretary find that regulations and other requirements imposed on tobacco products “are appropriate for the protection of the public health.”

S. Rep. No. 105-180, at 15 (1998).¹¹⁴

Indeed, at a 2007 hearing on tobacco legislation that contained a section nearly identical to FDCA § 910, Philip Morris USA’s Chairman and CEO noted in his written testimony:

“Importantly, tobacco products will not be regulated as a drug or device.”¹¹⁵

In addition to the specific “public health” considerations that Congress expressly directed FDA to consider under section 910, Congress’s invocation of a “public health” standard generally signals Congress’s intent to give FDA broad discretion in carrying out its regulatory functions under the Tobacco Act. *See, e.g., United States v. Bacto-Unidisk*, 394 U.S. 784, 798 (1969) (recognizing the “well-accepted principle that remedial legislation such as the Food, Drug, and Cosmetic Act is to be given a liberal construction consistent with the Act’s overriding purpose to protect the public health”). The Senate Report to S. 1415 (the precursor to the

¹¹⁴ The Senate Report on S. 1415 also described the major differences in that bill between the definition of substantial equivalence in the tobacco provisions as compared to the device provisions. *Id.* at 23.

¹¹⁵ Written Statement of Mike Szymanczyk, Chairman and CEO, Philip Morris USA, submitted to the Subcomm. on Health, House Comm. on Energy and Commerce (Oct. 3, 2007).

Tobacco Act) confirmed that Congress intended FDA to “weigh a variety of consequences resulting from possible new regulations on tobacco products” when making regulatory determinations under Chapter IX of the FDCA, and did not intend to limit the scope of FDA’s public health assessments. S. Rep. 105-180 at 18. Notably, recognizing the unusual breadth of the “public health” inquiry it authorized FDA to undertake when considering tobacco products, the Senate Report for S. 1415 cautioned that “The committee does not intend that this standard be applied to any other product regulated under the Act.” *Id.* at 19.

In short, Congress did not expressly or silently ratify, or intend to incorporate into the tobacco provisions, FDA’s interpretation of “substantial equivalence” from the device context. Rather, Congress spoke clearly – both in the statute and the legislative history – that “substantial equivalence” means something different in the context of tobacco products.

G. A tobacco product must be found substantially equivalent to a single predicate product in order to justify the granting of a substantial equivalence application.

In the guidance FDA issued on substantial equivalence, FDA properly interpreted the statutory language to mean that “a single predicate tobacco product should be used for comparison purposes, as FDA believes that a meaningful scientific comparison intended to determine whether the characteristics of the products are the same or are different but present no different questions of public health cannot be made between a new tobacco product and multiple tobacco products.”¹¹⁶

Several tobacco product manufacturers dispute this “plain meaning” interpretation and argue that manufacturers should be permitted to compare their products to multiple predicate products.¹¹⁷ Liggett and Lorillard argue that FDA should do so because the regulatory scheme developed for determining whether new medical devices are substantially equivalent to a predicate product permits comparison to multiple predicate devices. However, as demonstrated

¹¹⁶ Section 905(j) Reports: Demonstrating Substantial Equivalence for Tobacco Products, FDA 2010-D-0635. at 4.

¹¹⁷ Comments of Liggett Group LLC in FDA-2010-D-0635 at 7-8 (June 10, 2011). Comments of Lorillard Tobacco Company in 2010-FDA-D-0635 at 4 (February 4, 2011). Comments of Philip Morris USA Inc. and U.S. Smokeless Tobacco Company LLC in Docket No. FDA-2010-D-0635 at 4-5 (Feb. 8, 2011).

above, neither the statutory language, nor the legislative history, nor the legislative purpose of the provisions would support such an argument.

There are good reasons for FDA to interpret section 910 to require that any substantial equivalence showing be made against a single predicate product, even if, in the device context, FDA has permitted device makers to demonstrate equivalence to multiple predicates. In the device context, based on experience and the regulatory approval process FDA has a degree of confidence that, whatever the predicate(s), FDA has previously made a determination that each of the predicates is safe and effective for its intended use. The same is not true of tobacco products: FDA has not previously received and analyzed data about the chemical composition of smoke produced by the grandfathered tobacco product and it certainly has never—and could never—determine that such a product was “safe.” The tobacco companies’ position also ignores the complexity of tobacco products and the complex chemical interrelationship that occurs when a tobacco product is burned and its smoke inhaled. Moreover, the history of product modification in the medical device industry was altogether different from that in the tobacco industry. Development of new proven safe and effective medical devices facilitates the treatment and prevention of disease and the statutory policy established was designed to encourage innovation. By contrast, product modification in the tobacco industry, for decades unmoored from meaningful governmental review or oversight, has resulted in the proliferation of products that are deadly, addictive, and designed to promote initiation by underage users. There is no social value in permitting the marketing of a product simply on the ground that it combines the worst features of two or more existing products.

The companies argue that by restricting the comparison to a single product FDA would render the first prong of the definition in Section 910(a)(3) meaningless because “any new tobacco product that is not identical to a single predicate product would be regarded as having “different characteristics” and thus subject to the requirements of the second half of the substantial equivalence definition.¹¹⁸ There are at least two situations in which a new product could meet the first prong of the definition. If a predicate product is simply marketed under a different brand name, it would be a new product but would have identical physical characteristics. Alternatively, a new product could yield test results that are not identical to those

¹¹⁸ Comments of Lorillard Tobacco Company in FDA-2010-D-0635 at 4 (February 4, 2011).

of the predicate product but based on standards established by FDA are within a range sufficiently close to be considered “the same.” Nothing in the definition or its application indicates an intention to permit a new product that is not substantially equivalent to a *single* predicate product to be eligible to market a product pursuant to the procedure created by Section 905(j).

Liggett and Lorillard argue that a new tobacco product should be permitted to be marketed without meeting the requirements of section 910 if each different characteristic of the product is substantially equivalent to a characteristic in some predicate product. This argument suggests that the appropriate predicate product is the entire range of tobacco products currently on the market. As long as a new product has characteristics or toxicant yields in the smoke that, for each single characteristic or toxicant, do not exceed the bounds of the worst cigarette on the market for that individual characteristic or toxicant, the product would be considered substantially equivalent. Pushed to its extreme, this standard would set the acceptable limits for each individual toxicant in smoke based on the maximum level found in any cigarette brand on the market, with the level for each toxicant potentially being defined by a different brand. Thus, under the standard urged by Liggett and Lorillard, a new tobacco product could be, in the aggregate, more toxic, more carcinogenic, and more addictive than any cigarette ever marketed and still satisfy the “substantially equivalent” standard. Congress did not and could not possibly have envisioned such an outcome when it drafted the Tobacco Control Act and its use of the singular “predicate product” confirms that it did not. In considering the profile of a new product, FDA should consider the product as a whole in comparison to a single predicate product considered as a whole. No product should be permitted on the market simply because it does no more than combine the worst features of the worst products already on the market.

Philip Morris also submitted comments urging FDA to permit comparison of new products to “multiple predicates” approach to substantial equivalence for new tobacco products.¹¹⁹ To support its argument, Philip Morris misleadingly cited to the 2001 Institute of Medicine report, *Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction*. Contrary to Philip Morris’s contention, the IOM did not endorse a “multiple predicates”

¹¹⁹ Comments of Philip Morris USA Inc. and U.S. Smokeless Tobacco Company LLC in Docket No. FDA-2010-D-0635 at 4-5 (Feb. 8, 2011).

approach to regulating new conventional tobacco products. Rather, the IOM expressly stated that the responsibility for developing a standard against which to compare changes in conventional tobacco products “will rest with the regulatory agency.”¹²⁰ In addition, the ideas that the IOM committee raised as possible reference standards focused on *single* products (including “the most popular brand [and] the most (or least) harmful brand on specified dimensions”).¹²¹ Moreover, Congress did not adopt the recommendations of the 2001 IOM report on this issue. The standards contained in the 2009 legislation are different from those recommended in the 2001 IOM Report. Thus, Congress’s use of the singular “predicate tobacco product” in the statute, and FDA’s straightforward interpretation of that unambiguous language in the Guidance, is consistent with the approach contemplated by the 2001 IOM Report.¹²²

H. A change in the name of a product makes the product a new product.

In its Draft Guidance incorporating Responses to Frequently Asked Questions, FDA states that if a cigarette was marketed on February 15, 2007 but subsequently the name of the cigarette brand was modified or changed, the cigarette is a new tobacco product and subject to the premarket requirements of sections 905(j) and 910.¹²³ Philip Morris argues that a product’s name is not “part” of a Tobacco Product and that name changes do not require substantial equivalence reports or Section 910(b) submissions.¹²⁴ Philip Morris cites several provisions of the Tobacco Control Act that refer to brands and subbrands and argues from these provisions that the absence of a specific reference to brand names or product names in the definition of “tobacco product” that Congress did not intend to “regulate product names through these definitions.”¹²⁵

Philip Morris’s arguments miss the point. The term “tobacco product” is a defined term under the Tobacco Control Act, as is the term “new tobacco product.” All “new tobacco

¹²⁰ Institute of Medicine, *Clearing the Smoke*, at 223.

¹²¹ *Id.*

¹²² In fact, *Clearing the Smoke* was the impetus for a congressional hearing in 2003 on so-called “potential reduced exposure” tobacco products. Potential Reduced Exposure/Reduced Risk Tobacco Products: An Examination of the Possible Public Health Impact and Regulatory Challenges, H.R. Comm. on Government Reform (June 3, 2003). Thus, Congress may be presumed to have drafted the Tobacco Control Act – including the requirement that a new tobacco product demonstrate substantial equivalence to a single predicate tobacco product – with awareness of and due consideration for the IOM report.

¹²³ FDA, Draft Guidance, Answers to Frequently Asked Questions, Docket No. 2011-D-0147 at 5-6.

¹²⁴ Comments of Philip Morris USA Inc. and U.S. Smokeless Tobacco Company LLC in Docket No. FDA-2010-D-0147 at 8-10 (Nov. 8, 2011)

¹²⁵ *Id.* at 8

products” are “tobacco products.” Every tobacco product has a name (designated by a brand or a subbrand). The brand designation (i.e., the “Name”) of a tobacco product can have very substantial commercial importance. When a tobacco product manufacturer designates a product by a new brand name, it is not unreasonable for the FDA—and the world—to presume that that product is a new tobacco product—i.e., that it is somehow physically different in some respect from other tobacco products or that the new name is designed to change the target consumer base of the product. Thus, it is altogether reasonable for FDA to conclude that the indicium of a name change coincides with and identifies a “new tobacco product.” When the name of a product changes, therefore, the provisions of section 910 or 905(j), if applicable, take effect. In other words, by giving a product a name a tobacco product manufacturer undertakes the obligation to demonstrate whether the product so named meets the requirements of section 910 or section 905(j).

It is possible that the only thing about the newly named tobacco product will be the name. (In fact, some tobacco product manufacturers manufacture numerous private label brands as to which the physical objects bearing the different brand names are intended to be identical to each other.) In other words, the change in product name triggers an obligation to demonstrate whether or not the newly named product meets the requirements of Section 905(j) and is therefore “substantially equivalent” to the predicate product, or whether the newly named product fails to do so and is therefore required to meet the requirements of section 910. The same obligation would be triggered if the tobacco product manufacturer changes the physical characteristics of the product without changing its name. Philip Morris is therefore wrong when it alleges that the Tobacco Control Act creates a prior restraint against the renaming of a substantially equivalent product;¹²⁶ it merely creates an obligation on the part of the manufacturer to demonstrate that a renamed product is substantially equivalent to the predicate product, taking into account the research data the manufacturer is required to submit on the impact of the name change on, *inter alia*, non-smokers, former smokers and current smokers. Manufacturers have a reason for a name change and often it is to reach out to a new market.

¹²⁶ Comments of Philip Morris USA Inc. and US Smokeless in Docket No. FDA-2011-D-0147 at 8-9 (November 8, 2011).

I. Any change in a product constitutes a “modification.”

As discussed above, Philip Morris argues that some changes to an existing product should not be deemed to “modifications” and hence that some such changes would not render the changed product a “new product.”¹²⁷ This argument is inconsistent with the statute and inconsistent with the FDA’s draft guidance. All changes to a product are “modifications” that render the product a new product and trigger the applicability of sections 905(j) and 910. Section 905(j)(3) statute creates a mechanism for classifying certain modifications as “minor modifications.” If a tobacco product manufacturer believes a certain modification has no affect on the disease risk posed by a product, or on non-smokers or former smokers or on the intent of smokers to quit, they are free to provide scientific data to support a request to seek classification of the modification as a “minor modification.” This procedure is far preferable to deeming certain product changes not to be “modifications” because such a procedure affords the regulatory agency an opportunity to evaluate whether in fact certain changes can be conclusively presumed not to affect the exposure risk or the disease risk posed by the product.

J. Use by a manufacturer of another manufacturer’s product as a predicate product.

Commonwealth argues that given the amount of information required by FDA’s draft guidance to establish substantial equivalence it is unlikely that a manufacturer would be able to use a product manufactured by a different manufacturer as a predicate product, at least in the absence of cooperation from the manufacturer of the predicate product.¹²⁸ It is certainly more difficult for a manufacturer to do so. Whether it is more difficult for a manufacturer to develop sufficient information about the predicate product to make the necessary demonstration should not be a consideration in FDA’s development of procedures appropriate for the protection of the public health. It is the obligation of the manufacturer to meet the scientific burden. If it cannot, its product should not be marketed.

¹²⁷ Comments of Philip Morris USA, Inc. and US Smokeless LLC in FDA-2010-N-0646 at 6 (March 22, 2011).

¹²⁸ Comments of Commonwealth Brands, Inc., et al., in FDA-2010-D-0635 at 7 (March 3, 2011).

III. Scientific evidence proffered by the industry does not show that increased levels of harmful or potentially harmful constituents do not raise different questions of public health.

R.J. Reynolds argues that “scientific evidence does not establish that variations in ingredient composition and design parameters among cigarettes currently on the market increase the health risks associated with the use of tobacco products.”¹²⁹ From this proposition, Reynolds argues that variations in ingredient composition and design parameters should be deemed “substantially equivalent” as long as such changes are “within the established range of ingredients and design parameters associated with legally marketed tobacco products.”¹³⁰ Philip Morris makes a similar argument, contending that “new tobacco products with conventional designs comprising new combinations of ingredients, ingredient levels and materials used in marketed tobacco products would have the same characteristics as those already marketed products in terms of smoke toxicity.”¹³¹ This argument suggests that the appropriate predicate product is the entire range of tobacco products currently on the market. If this argument were accepted, as long as a new product has characteristics or toxicant yields in the smoke that, for each single characteristic or toxicant, do not exceed the bounds of the worst cigarette on the market for that individual characteristic or toxicant, the product would be considered substantially equivalent. Pushed to its extreme, this standard would set the acceptable limits for each individual toxicant in smoke based on the maximal level found in any cigarette brand on the market, with the level for each toxicant potentially being defined by a different brand.

A. The standard proposed by Reynolds misrepresents what is known scientifically and distorts how scientific evidence is appropriately interpreted.

Contrary to the argument made by Reynolds, scientific evidence does NOT establish that the known variations in ingredient amounts, smoke composition and design parameters for cigarettes currently on the market do not result in differences in the health risks.

¹²⁹ Comments of R.J. Reynolds in FDA-2010-N-0646 at 9 (March 21, 2011).

¹³⁰ *Id.* at 33.

¹³¹ Comments of Philip Morris USA and US Smokeless LLC in FDA-2010-D-0635 at 6 (Feb. 8, 2011).

All tobacco companies now concede that all cigarettes cause tobacco-related disease. FDA has identified 93 harmful and potentially harmful constituents in tobacco products. Most of these constituents are carcinogenic or otherwise toxic.¹³² It is generally accepted that exposure to these smoke toxicants causes tobacco related diseases, and there is overwhelming evidence that higher levels of human exposure to the combination of these toxicants in smoke increases disease risks compared to lower levels of exposure to lower levels of the same mix of toxicants.¹³³ This is amply demonstrated by the data on increasing disease risks with increasing cardiopulmonary disease or cotinine levels as measures of whole smoke exposure or by increasing risk for lung cancer among those with higher exposure to TSNAs even controlling for measures of whole smoke exposure.¹³⁴ Reynolds' argument is based on the absence of evidence demonstrating differences in disease risk across brands that have different design characteristics or levels of toxicant delivery to the smoker. To the extent that there is an absence of evidence demonstrating a difference in disease risks for different brands or brand characteristics (other than for TSNAs), that absence of evidence exists because it has not been possible to examine the question of difference in disease risks across brands prior to the enactment of the Tobacco Control Act. The formulae for brands and sub-brands of cigarettes have been—and remain-- a zealously maintained trade secret. It has been impossible for researchers to know the ingredients—and their quantities—in cigarette brands in a manner that would have enabled them to define the differences in human exposure likely to result from the use of various brands. Moreover, prior to the enactment of the Tobacco Control Act, cigarette manufacturers were free to make whatever changes they wished to their products without disclosure; and there was no way for the scientific community to determine whether a particular combination of smoke

¹³² 77 F.R. 20034-37 (April 3, 2012) Department of Health and Human Services, Food and Drug Administration, Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Established List, Docket No. FDA-2012-N-0143.

¹³³ U.S. Department of Health and Human Services (HHS), *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking Attributable Disease: A Report of the Surgeon General*, Office on Smoking and Health, 2010.

¹³⁴ Church TR, Anderson KE, Caporaso NE, Geisser MS, Le CT, Zhang Y, et al. A prospectively measured serum biomarker for a tobacco-specific carcinogen and lung cancer in smokers. *Cancer Epidemiol Biomarkers Prev* 2009 Jan;18(1):260-6.

Yuan JM, Koh WP, Murphy SE, Fan Y, Wang R, Carmella SG, et al. Urinary levels of tobacco-specific nitrosamine metabolites in relation to lung cancer development in two prospective cohorts of cigarette smokers. *Cancer Res* 2009 Apr 1;69(7):2990-5.

toxicants present in Brand A on a given date was the same as that for Brand A on a different date. The enactment of the Tobacco Control Act, which for the first time requires detailed reporting of tobacco product ingredients and smoke constituents by brand and subbrand—and disclosure of such information in a form that researchers can use—would make meaningful analysis across brands possible for the first time.

Reynolds argues that the absence of scientific evidence about the specific relative disease risk posed by different brands, directly attributable to its own refusal to disclose sufficient information to permit such analysis, justifies a conclusion that if such differences across brands were examined no differences would be found. The basic rules of logic for scientific inference provide that in the absence of evidence examining an effect one cannot establish the absence of an effect. Defying this basic logic, Reynolds now claims that the absence of such evidence demonstrates that no such difference exists. Reynolds argues that, because it claims science has not yet proven that the particular combination of constituents associated with one brand is more likely to cause tobacco-related disease than the particular combination of constituents associated with another brand, differences in toxicant levels of harmful and potentially harmful constituents within the range of currently marketed cigarettes have no effect on the health risk such products present. This argument fundamentally misrepresents the state of the existing knowledge and the fact that the statute places the burden on the tobacco manufacturer not the FDA.

It is reasonable for FDA to conclude that increasing a subject's exposure to toxicants increases the risk of disease. There are 69 known or probable carcinogens in cigarette smoke¹³⁵ as well as many other toxicants, and most of these toxicants have clear dose response relationships for their toxicity established in animal studies. The levels of these carcinogens and other toxicants found in machine generated smoke using standardized smoking protocols varies substantively across different brands of U.S. style cigarettes offered on the international market,¹³⁶ and there is every reason to believe that similar variation will exist for the cigarettes

¹³⁵ NCI, *Risks Associated with Smoking Cigarettes with Low Machine-Measured Yields of Tar and Nicotine*, Smoking and Tobacco Control Monograph No. 13, Bethesda, MD: HHS, National Institutes of Health, National Cancer Institute, NIH Pub. No. 02-5074, October 2001, http://dcccps.nci.nih.gov/tcrb/monographs/13/m13_5.pdf

¹³⁶ Counts ME et al. (2004) Mainstream smoke toxicant yields and predicting relationships from a worldwide market sample of cigarette brands: ISO smoking conditions. *Regulatory Toxicology and Pharmacology*, 39:111–134.

on the U.S. market as they are reported to the FDA. With the exception of TSNA's (where an independent effect of differences in exposure levels has been demonstrated) variations in the exposures to different carcinogen or other toxicant exposures across brands have not been adequately examined. It is for that reason that Congress placed the burden on the manufacturer to prove to FDA whether or not the expected differences in smoke constituent levels might result in meaningful differences in human disease risks.¹³⁷ To the extent that relationships between existing variations in toxicant yields and human disease outcomes have not been examined for most toxicants does not indicate that differences in disease risk do not exist. In fact the opposite is true: existing animal toxicity data coupled with the variation known to exist across cigarette brands in toxicant yields strongly suggest that differences in human disease risks are likely to exist.¹³⁸ However, it is only since the FDA has required the disclosure of toxicants in smoke and changes in cigarette design and manufacturing that the government has the data to begin the process of examining the extent to which differences across brands translate into differences in disease risks.

Examination of the differences across brands in the disease risks produced by differences in smoke toxicant composition is complicated by the large number of toxicants, the potential for interactions among those toxicants, and the reality that differences in how the cigarette is smoked can lead to marked differences in the composition of the smoke generated. These complexities also impact assessment of the disease risks likely to result from additives used to manufacture cigarettes. Reynolds argues that additives have been examined by adding them as a single constituent to a standard cigarette which then generated no meaningful differences in toxicity.¹³⁹ Putting aside Reynolds's blatant misrepresentation of what these studies actually show and the appropriate interpretation of the actual evidence, one of the common purposes of tobacco

Counts ME et al. (2005) Smoke composition and predicting relationships for international commercial cigarettes smoked with three machine-smoking conditions. *Regulatory Toxicology and Pharmacology*, 41:185–227.

¹³⁷ World Health Organization, Study Group on Tobacco Product Regulation, *The Scientific Basis of Tobacco Product Regulation: Report of a WHO Study Group*. WHO Technical Report Series #951. World Health Organization, Geneva Switzerland. 2008.

¹³⁸ *Id.*

¹³⁹ Comments of R.J.Reynolds Tobacco Company in FDA-2010-D-0646 at 34 (March 21, 2011).

additives is to change the character of the smoke;¹⁴⁰ the burden is on the manufacturer to develop methods satisfactory to FDA to predict how a change in one additive will interact with other additives to influence smoking behavior and resultant smoke composition. Additives are often used singly and in combination to alter the perception by the smoker of the smoke, which in turn may alter the way the cigarette is smoked and the depth of inhalation of the smoker.¹⁴¹ Other characteristics of the product, including other manufacturing components or changes in product design can also influence the delivery of toxicants and affect disease risk. As described above, differences in the pattern of smoking can generate differences in the toxicant composition of the smoke. Consequently, the addition of—or a change in the level of—an ingredient that is not itself toxic or carcinogenic may affect the disease risk of the product by altering the delivery of other constituents. To suggest that these concerns can be dismissed because many of the additives are on the GRAS list or have been examined as single constituent changes in standard cigarettes disregards the current scientific understanding of the complexity of smoke generation, the effect of combustion and the known interactions between smoke constituent levels and smoking behavior.¹⁴²

A cigarette product can be evaluated only by studying the effect of all the characteristics of a product in combination. In assessing whether a new product is substantially equivalent to a predicate product, the guidance proposes to compare the characteristics of the product and the composition of the smoke generated under standardized conditions. Measurement of smoke yields under standardized conditions is intended to demonstrate performance of the product under two specified smoking protocols, neither of which is intended to mimic smoking behavior of actual smokers. If the design characteristics, composition and performance under standardized conditions of smoke generation are statistically identical, it is reasonable to consider that fact in determining whether the new product is substantially equivalent to the predicate product. To the extent that any of the characteristics, composition or performance under standardized conditions

¹⁴⁰ Rabinoff, MC, et al., “Pharmacological and Chemical Effects of Cigarette Additives,” *American Journal of Public Health* Vol 97, No. 11, November 2007; Bates, C, et al., “Tobacco additives, Cigarette engineering and nicotine addiction,” July 14, 1999.

¹⁴¹ Bates, C, et al., “Tobacco additives, Cigarette engineering and nicotine addiction,” July 14, 1999; U.S. Department of Health and Human Services (HHS), *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking Attributable Disease: A Report of the Surgeon General, Office on Smoking and Health*, 2010.

¹⁴² A component that is generally recognized as safe when ingested as a food product may be carcinogenic or toxic when combusted.

of smoke generation (particularly for increases in smoke toxicant levels in the smoke) differ from the predicate product, the evidence does not allow a direct demonstration of substantial equivalence based on identical performance, and a judgment needs to be made as to whether the differences observed raise new issues of public health concern. This judgment cannot be made based on the machine testing data alone. Thus, while machine testing data is relevant, it may not be dispositive.

In order to assess whether a product that performs differently under standardized conditions does, or does not, raise new questions of public health concern, it is necessary to assess its performance under conditions similar to those of its actual use. The potential for differences in actual smoking patterns to produce differences in smoke toxicant levels and differences in the relative concentrations of smoke toxicants from those produced by the proposed machine testing protocols is real and needs to be tested. Interactions among and between the mix of smoke toxicants and cigarette additives and the likely effect of additives and design features on smoking patterns defy easy prediction of what will happen with human use. At a minimum, an assessment of the actual pattern of use of the product using smoking topography approaches in comparison to the predicate product would be necessary. Smoke toxicant levels measured using the smoking pattern observed among human smokers (median plus 10 and 90 percent of the total smoke generated) would also be needed to assess whether differences are observed which raise new public health concerns. If the product and the predicate product differ under standardized testing, it is essential to assess whether those differences manifest as differences raising a new public health concern under conditions of actual use.

Disease risk is affected by smoking topography.¹⁴³ As has been demonstrated with regard to “light” cigarettes, the actual exposure of smokers to toxic constituents depends not only on the level of toxicants in the cigarette smoke but also on the way cigarettes are smoked and the total quantity of toxicants a smoker is exposed to by his particular pattern of smoking.¹⁴⁴ The

¹⁴³ U.S. Department of Health & Human Services. “The Health Consequences of Smoking: a Report of the Surgeon General,” May 27, 2004, http://www.cdc.gov/tobacco/data_statistics/sgr/2004/complete_report/index.htm. U.S. Department of Health and Human Services (HHS), How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking Attributable Disease: A Report of the Surgeon General, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2010.

¹⁴⁴ NCI, *Risks Associated with Smoking Cigarettes with Low Machine-Measured Yields of Tar and Nicotine*, Smoking and Tobacco Control Monograph No. 13, Bethesda, MD: HHS, National Institutes of Health, National Cancer Institute, NIH Pub. No. 02-5074, October 2001, http://dceps.nci.nih.gov/tcrb/monographs/13/m13_5.pdf

level of various non-toxic ingredients in cigarettes (particularly those that influence the sensory experience of the smoker), differences in other cigarette components, and changes in product design elements may influence smoking topography, and therefore may influence the exposure of smokers to harmful and potentially harmful constituents that may influence the disease risk.

B. The studies cited by the companies do not provide support for the conclusion that changes in the levels of ingredients have no effect on disease risk.

Several tobacco product manufacturers argue that additives do not make tobacco products any more or less dangerous to health. For example, Philip Morris argues that “tobacco itself drives the biological activity of cigarette smoke and this biological activity is not impacted by the addition of ingredients commonly used.”¹⁴⁵

Reynolds cites several studies evaluating “the effects of ingredients added to tobacco on the chemical composition and in vitro genotoxicity and cytotoxicity of mainstream tobacco smoke” to support its assertion that additives do not increase the level of toxic, carcinogenic, or addictive constituents.¹⁴⁶ A recently published scientific critique of the methodology of these studies, however, demonstrates that their conclusions are not scientifically sound.¹⁴⁷ The studies at issue were designed by Philip Morris scientists in 1997 in a program known as Project Mix, and resulted in four papers accepted for publication in Food and Chemical Toxicology in 2001 and 2002. Project MIX examined the potential chemical and biological effects of 333 additives used in cigarette manufacturing that were selected because they were representative of flavors used throughout the world by Philip Morris. Three different groupings of additives were tested against a control cigarette containing only tobacco. The chemical analysis of the smoke tested for 51 smoke constituents but excluded a substantial number of constituents of substantial public health concern because they cause carcinogenic and non-carcinogenic disease in animals and humans. Rather than reporting test results on a per-cigarette basis, the researchers, at the request of Philip Morris, altered the study protocol to report and synthesize results on a per total particulate matter (“TPM”) basis. Emphasizing the per-TPM results permitted the study to

¹⁴⁵ Comments of Philip Morris USA Inc. and Us Smokeless LLC in FDA-2010-D-0646 at 3 (March 22, 2011).

¹⁴⁶ Comments of R.J.Reynolds Tobacco Company in FDA-2010-D-0646 at 34 (March 21, 2011).

¹⁴⁷ Wertz SM, et al., The Toxic Effects of Cigarette Additives. Philip Morris’ Project Mix Reconsidered: An Analysis of Documents Released Through Litigation. PLoS Medicine, vol. 8, issue 12, December 2011.

ignore the fact that the test cigarettes produced higher levels of TPM than the control cigarettes.¹⁴⁸ It was on this basis that the Project MIX study concluded that the additives did not add to the toxicity of smoke. However, as the critique notes, smokers do not smoke cigarettes to titrate their TPM exposure but rather to obtain certain levels of nicotine. Presenting the results on a per-unit nicotine basis, 37 of the 51 analytes increased in at least one of the three ingredient groups and on a per-cigarette basis, 31 of the 51 increased.

The critique also noted that the animal toxicity results were based on a small number of rats in each experiment. When the authors of the critique re-examined what the statistical conclusions would have been had Project MIX found their results on the basis of a sample size of 50 rats. This analysis yielded the conclusion that a better powered study “would have detected a much broader range of biological effects associated with the additives,” suggesting that it substantially underestimates the toxic potential of cigarette smoke and additives. Moreover, the critique also found methodological problems with the animal toxicology studies that result in a substantial understatement of the effect of additives on toxicity.¹⁴⁹ (The critique concluded that a proper interpretation of the data from the Project MIX study would conclude that “many of the toxins in cigarette smoke increased when additives are put in cigarettes . . . and that the data show many adverse biological consequences.”¹⁵⁰

Philip Morris’s comments also reference a series of studies published in *Inhalation Toxicology* discussing the testing of cigarette ingredients and concluding that “ingredients used in modern cigarettes do not substantially alter smoke toxicity.”¹⁵¹ These studies also purport to show that the additives do not substantially alter the toxicity of mainstream smoke. However, the methodology of the studies—to study the effect of individual additives on mainstream smoke—is not designed to produce meaningful results. Given that currently marketed cigarettes contain hundreds of different ingredients, it is not surprising that the introduction of a single additional ingredient would have a small effect on mainstream smoke. By contrast, the addition

¹⁴⁸ As the Wertz critique points out, as long as the amount of a toxin in the smoke of a test cigarette increased by less than the amount TPM increased in that cigarette, the ratio would drop even if both the toxin and TPM increased with the additives.

¹⁴⁹ Wertz SM, et al., *The Toxic Effects of Cigarette Additives. Philip Morris’ Project Mix Reconsidered: An Analysis of Documents Released Through Litigation*. *PLoS Medicine*, vol. 8, issue 12, December 2011.

¹⁵⁰ *Id.* at 10.

¹⁵¹ Comments of Philip Morris USA, Inc. and US Smokeless LLC in Docket No. FDA-2010-D-0635 at 6, (Feb. 8, 2011).

of particular combinations of hundreds of ingredients in the aggregate might well have substantial effects. In evaluating the effects on additives and ingredients on smoke constituents, more meaningful results would be obtained by examining the effects of ingredients in the combinations in which they exist in commercial cigarettes. The results of such examinations, in studies properly performed and analyzed, might well be quite different from those obtained in studies of the effects of single additives in isolation.

Moreover, the studies repeated many of the same methodological errors that characterized the Project Mix studies. Similarly to Project Mix studies, in the 90-day rat inhalation study the levels of smoke exposure were adjusted to expose all rats to the same level of TPM. As noted above, such an adjustment is inappropriate since smokers do not calibrate their smoking to achieve a level of TPM. In addition, cigarette weights were kept constant with the result that as the amount of the tested ingredient increase, the amount of tobacco in the tested cigarettes decreased. It does not appear that the authors of the study made any adjustment in analyzing their test results to account for this reduction in the amount of tobacco. In addition, the authors of the study inappropriately limited the exposure period to 90 days in ostensible reliance on a paper written by another Philip Morris researcher, Christopher Coggins.¹⁵² However, the Coggins paper actually states that the preferred assay is 5 months (150 days) with a 4-month follow-up period.¹⁵³ However, neither of these exposure periods would meet the requirements of the National Toxicology Program that uses a standard protocol to evaluate carcinogenicity in mice and rats and requires a 2-year exposure. NTP conducts 90-day “pre-chronic” studies to evaluate general toxicity and as a range-finding exercise for the 2-year study. The use of a 90-day exposure period is not consistent with the NTP program.¹⁵⁴ In addition, the Philip Morris tests used far fewer animals than the number recommended by NTP and thus lack the power to detect potential effects of the tested materials. These shortcomings make it wholly inappropriate for FDA to give credence to these results.

As is typical of industry-sponsored research, methodologies and references rely almost exclusively on other industry-sponsored research which incorporates questionable methods.

¹⁵² Coggins, CRE, A further review of inhalation studies with cigarette smoke and lung cancer in experimental animals, including transgenic mice, *Inhalation Toxicology* 2010; 22(12): 974-983.

¹⁵³ *Id.* at 981.

¹⁵⁴ <http://ntp.niehs.nih.gov/ntp/Test Infor/Final NTPToxCarSpecsJan.2011.pdf>.

Such self-referential methodologies can hardly provide an adequate scientific basis for regulatory policy. Rather, studies such as these are designed to produce only the results desired by their sponsors.

An important threshold question for FDA in determining whether a study provides information useful in the regulatory process is how sensitive a study needs to be “negative” (i.e., not finding a statistically significant difference before one can conclude that “equivalence” has been established. This is a particular problem because most statistical hypothesis testing (which gives rise to P values and "statistical significance") implicitly assumes that the investigator wants to find a difference and so is focused on estimating the probability that a reported difference is a random finding rather than a real effect (i.e., a false positive conclusion). The issue regarding conclusions of "substantial equivalence" is the other side of the coin, namely controlling the risk of a false negative conclusion (i.e., concluding that there is no difference when one actually exists but is obscured by random noise in the data). This is what is called statistical “power” and is used to decide how big studies need to be. The power also depends on how big an effect is deemed to be “worth” detecting. It is important that FDA require that applicants report the power to detect an effect and how large that effect size is so that the agency can judge whether studies that do not reach “statistical significance” actually support the conclusion of “no effect” on “substantial equivalence.”

A number of the studies cited by Reynolds in support of its assertion that additives have no effect on toxicity fail to disclose the size of the sample studied and thus make it impossible to know what the power to detect a given effect size is. This omission is critical because an underpowered study cannot produce results sufficiently accurate to inform a regulatory decision “no effect” (i.e., “substantial equivalence”). Before the results of such studies can appropriately be considered FDA must establish minimum requirements for the power and effect size of such studies and consider only studies that meet such requirements. This issue is discussed more fully in comments filed in this docket by Professor Stanton Glantz of the University of California at San Francisco.

Commonwealth suggests that the only relevant measure is tar and nicotine in fresh, whole tobacco smoke.¹⁵⁵ This argument, if accepted, would perpetuate the fraud that led consumers to believe that light cigarettes were less harmful than full-flavored cigarettes. The measures suggested by Commonwealth are altogether inadequate to recognize differences among brands that may be significant.

Finally, as previously discussed, the industry's narrow focus on toxicity and disease risk to an individual who is already smoking is inconsistent with the public health standard in the statute.

C. Internal product evaluation programs of the companies do not provide credible judgments regarding substantial equivalence.

Reynolds argues that its own “Stewardship Program” and similar programs of other major tobacco product manufacturers already “appropriately and effectively monitor and evaluate changes in tobacco product design to ensure that any changes made to the design. . .do not increase the inherent risks associated with the product when used as intended.”¹⁵⁶ Other manufacturers make similar arguments.¹⁵⁷

The historical record provides massive evidence that the tobacco product manufacturers defrauded the public over the course of many decades by arguing that their product testing and design programs were designed to protect the public health. On the contrary, such programs have been designed with the sole aim of maximizing profits from the sale of cigarettes. The landmark decision of the US District Court for the District of Columbia in *U.S. v. Philip Morris USA, Inc.* demonstrates these facts in exhaustive detail. The court concluded,

. . . There is overwhelming evidence that even though Defendants have known internally about addiction for decades, they have endeavored to keep the extensive research and data they had accumulated out of the public domain and out of the hands of the public health community by denying that such data existed, by refusing to disclose it, and by shutting down or censoring laboratories and research projects which were investigating the mechanisms of nicotine.

¹⁵⁵ Comment of Commonwealth Brands, Inc. in FDA-2010-D-0635 at 3 (March 18, 2011).

¹⁵⁶ Comments of R.J. Reynolds Tobacco Company in FDA-2010-N-0646 at 12 (March 21, 2011).

¹⁵⁷ See, e.g., CITMA's suggestion that FDA should leave it to the manufacturers to decide when it is necessary for a substantial equivalence filing to be made. Philip Morris comments in FDA-2010-D-646 discussing its program of “product integrity.”

Defendants' false and misleading statements relating to addiction continue even today. . .

. . .Over the course of approximately fifty years, . . .Defendants. . . took the following actions in order to maintain their public positions on smoking and disease-related issues, nicotine addiction, nicotine manipulation, and low tar cigarettes, in order. . . . to avoid regulation which they viewed as harmful: they suppressed, concealed, and terminated scientific research; they destroyed documents including scientific reports and studies; and they repeated and intentionally improperly asserted the attorney-client and work-product privileged over many thousands of documents to thwart disclosure. . . .[W]e can never know the full extent of the evidence destroyed and lost to public view.

449 F. Supp. 2d 1, 307, 308, 839.

Based on this record, there is no basis for tobacco companies to argue that their internal testing programs are capable of protecting the public against increased risk of tobacco-related death and disease. Given the record of fraud and misconduct so conclusively documented in *US v. Philip Morris*, it is incredible that any tobacco company would suggest to FDA that determinations of such importance to the public health should be left to them. The "Stewardship Program" proposed by Reynolds is only the latest iteration of the industry's ongoing conspiracy to defraud the public and to avoid any significant change in the manner in which they conduct their business. In essence, Reynolds is arguing that the companies' current programs already provide sufficient protection for the public health. If this were true, we would not face a situation in which 443,000 Americans die each year from tobacco-related disease.

If the companies were performing tests sufficient to inform them of increased levels of risk, they would already have available from their own internal testing virtually all the information FDA is seeking in the draft guidance. The fact that such information has never been developed is conclusive evidence that the companies' programs have never been concerned with minimizing consumers' exposure to disease risk from their products. The purpose of the Tobacco Control Act was not to perpetuate the status quo in the marketing of tobacco products, but to give FDA the tools necessary to change it in order to protect the public health.

D. The existing ingredient reporting system under FCLAA provided no protection to consumers.

Reynolds argues that the reporting of ingredients by manufacturers pursuant to the FCLAA provides some evidence that the Department of Health and Human Services had somehow concluded that the addition of such ingredients did not pose a threat to public health.¹⁵⁸ This argument has no merit. The reporting required by FCLAA merely required companies to list all the ingredients added to any of the cigarettes they sold. As Reynolds concedes, the information reported to the CDC did not identify which companies added which ingredients, did not specify which brands of cigarettes contained which ingredients, and did not list the quantity of any ingredient added. Moreover, none of this information was publicly disclosed. The information provided to the Secretary provided no basis whatsoever to determine the effect of the addition of ingredients on the health risks to consumers. On the contrary, the companies zealously guarded the information that only they possessed concerning the contents of their brands and it was not until the enactment of the Tobacco Control Act that this situation changed. Having made it impossible for the Secretary to make any effective use of the meaningless information it provided, Reynolds now argues that the absence of reports concluding that ingredients posed a threat to public health is somehow significant. To the contrary, all this experience demonstrates is that effective analysis is impossible unless the companies provide brand-specific information on ingredients and product design as required by the Tobacco Control Act. Far more informative are the numerous reports of the Surgeon General issued by CDC during these years detailing how cigarettes, as designed and configured by the tobacco product manufacturers and containing whatever ingredients they chose to add, brought death and disease to millions of Americans. The 2000 Report of the Surgeon General succinctly describes CDC's views regarding the adequacy of information on additives:

Additives to tobacco products are of uncertain safety when used in tobacco. Knowledge about the impact of additives is negligible and will remain so as long as brand-specific information on the identity and quantity of additives is unavailable.¹⁵⁹

¹⁵⁸ Comments of R.J. Reynolds Tobacco Company in FDA-2010-D-0646 at 11-12 (March 21, 2011).

¹⁵⁹ Reducing Tobacco Use, a Report of the Surgeon General, Centers for Disease Control and Prevention, United States Department of Health and Human Services, chapter 5, p. 261 (2000).

The conclusions Reynolds thus seeks to draw on the basis of the pre-2009 ingredient disclosure program are thus wholly unwarranted.

E. Tariff classifications provide no basis for a finding of substantial equivalence.

Commonwealth argues that in the absence of specific information about the characteristics of the predicate tobacco products, tariff classifications include generic tobacco product characteristics that can be used to support a finding of substantial equivalence.¹⁶⁰ The distinctions drawn by the tariff classifications are extremely crude and were never intended to classify tobacco products according to their relative health risks. The kind of information included in tariff classification does not begin to provide sufficient information to draw this conclusion. Tariff information contains no data regarding the content of harmful and potentially harmful constituents in tobacco or the relative health risks posed by different products. Since the reason for instituting a strict regulatory program for new products is to protect the public health, the absence of such data in tariff information renders it useless for this purpose.

F. Arguments Based on Specifications of Predicate Products.

Philip Morris argues that a product should not be considered to have been “modified” if it is “produced within specifications that existed prior to February 15, 2007.”¹⁶¹ Philip Morris argues that such an approach would permit a range of adjustments to maintain consistent product characteristics. By redefining “modifications,” however, Philip Morris would render the entire regulatory structure for determining substantial equivalence inapplicable to any product alleged by the manufacturer to meet this requirement. Such an approach would be inconsistent with the statutory requirements. As the FDA has properly stated, any change in a product constitutes a “modification” and makes the product a “new tobacco product.”¹⁶² Moreover, Philip Morris’s suggested approach would fail to protect the public health. Unless the specifications of the original product designated the levels of all harmful and potentially harmful constituents—a highly unlikely possibility—the new product might increase the danger to public health even if fit the specifications of the predicate product. Moreover, a specification sheet produced by a

¹⁶⁰ Comments of Commonwealth Brands Inc., et al. in FDA-2010-D-0635 at 5(March 3, 2011).

¹⁶¹ Comments of Philip Morris USA Inc. and U.S. Smokeless Tobacco Company LLC in Docket No. FDA-2010-D-0635 at 4 (Feb. 8, 2011);

¹⁶² FDA, Guidance for Industry and FDA Staff, Section 905(j) Reports: demonstrating Substantial Equivalence for Tobacco Products, January 5, 2011.

tobacco product manufacturer for a predicate product would not demonstrate that the actual product met the specifications. Thus, FDA has properly required actual product testing to demonstrate the levels of harmful and potentially harmful constituents in both the predicate product and the new tobacco product. If a tobacco product manufacturer demonstrates that the predicate product, as actually marketed on February 15, 2007, actually had smoke constituents that spanned a range, a new product might be deemed substantially equivalent if its constituents fell within such range.

G. Establishment of “good manufacturing practices” is no substitute for effective implementation of rigorous requirements for substantial equivalence.

Reynolds argues that the FDA’s authority to prescribe and enforce good manufacturing practice requirements under Section 906(e) of the Tobacco Control Act is “a more acceptable mechanism for FDA to regulate routine consistency- maintaining adjustments.”¹⁶³ Reynolds’ suggestion that FDA should impose “a design control requirement on manufacturers to properly qualify and document all design changes, including routine, consistency-maintaining adjustments” is far from adequate to ensure that the products resulting from such adjustments do not create an increased the risk of tobacco-related disease. Regardless of the reason for design changes in a tobacco product, such changes can have the effect of increasing the disease risk posed by a tobacco product if they result in an increase in the delivery of toxic, carcinogenic, or addictive constituents to the consumer. Establishment of procedures for good manufacturing practices cannot eliminate this risk and are no substitute for appropriate exercise of FDA’s regulatory authority under Section 905(j). The purpose of good manufacturing practices is to ensure that nothing in the manufacturing process and the handling of the product in the production facility inadvertently produces a product other than one meeting the relevant specifications. Different regulatory requirements are needed to ensure that products meeting specification do not increase the level of risk.

¹⁶³ Comments of R.J. Reynolds Tobacco Company in FDA-2010-D-0646 at 2, 27,31 (March 21, 2011).

IV. Arguments regarding the testing of products

A. Machine testing provides essential information in the evaluation of substantial equivalence.

Section 8 of the Draft Guidance provides instructions for listing such constituents and provides for reporting of the levels of all harmful and potentially harmful constituents showing quantitative levels in smoke using both the International Organization for Standardization (ISO) and Canadian Intense smoking regimens. The Draft Guidelines also provide for the use of alternative regimens if the manufacturer chooses to use them. The Draft Guidelines call, *inter alia*, for the reporting of the level of each constituent, the level measured for both the new product and the predicate with 95% confidence intervals, the number of replicates and the method of measuring.

FDA has established a list of 93 harmful and potentially harmful constituents.¹⁶⁴ In its notice establishing the list of constituents, FDA stated that it would require reporting pursuant to section 904(a) only for 20 of the 93 constituents. FDA noted, however, that substantial equivalence filings should provide information for all constituents on the list. Such testing is an essential element in establishing substantial equivalence.

In their comments on FDA's draft guidance for substantial equivalence, the tobacco companies mischaracterize the scientific basis for product regulation. Although prominent tobacco scientists have criticized overreliance on machine-measured levels of toxicants for providing information to consumers, they nevertheless agree that machine testing provides useful information to regulators and consumers in assessing toxicant levels in mainstream cigarette smoke.¹⁶⁵ Moreover, given the then existing availability of data, the WHO Study Group on Tobacco Product Regulation ("TobReg) concluded that "currently available regulatory strategies are limited to product performance standards based on product ingredients and emissions in machine-generated smoke rather than strategies based on measures of exposure or harm."¹⁶⁶

¹⁶⁴ 77 F.R. 20034-37 (April 3, 2012), Food and Drug Administration [Docket No. FDA-2012-N-0143]\ Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Established List.

¹⁶⁵ WHO Study Group on Tobacco Product Regulation, Report on the Scientific Basis of Tobacco Product Regulation (2007), pp. 45-46.

¹⁶⁶ Id.

The Committee found

Mandated lowering of levels of toxicants per milligram of nicotine in cigarette smoke will make regulation of cigarettes consistent with other regulatory approaches to mandate reduction of known toxicants in products used by humans. Reducing the level of toxicants in products intended for human use is a widely accepted regulatory practice. The anticipated outcome is a marketplace that excludes those brands with the highest levels of toxicants.¹⁶⁷

These findings, although addressed toward establishment of product standards based on maximum permissible levels of toxicants, are relevant for implementing standards for substantial equivalence. Establishment of rules that would prohibit increases in the levels of machine-measured toxicants in tobacco products over the levels prevailing in predicate products would at least prevent product changes that plausibly could increase the disease risk of tobacco products. By contrast, establishment of a policy that permitted such increases would unnecessarily expose consumers of tobacco products to heightened levels of risk.

B. Alleged lack of laboratory capacity.

Lorillard objects to the breadth of the reporting requirement because of an alleged lack of laboratory capacity necessary for the analysis of such constituents.¹⁶⁸ This is a remarkable admission. It means that manufacturers have put thousands of products on the market without having tested them for the content of all harmful and potentially harmful constituents (i.e., toxicants, carcinogens, and addictive substances) and the fact that they believe it would be appropriate for them to continue to do so speaks volumes about the tobacco industry's continuing disregard for safety. It is impossible for the tobacco companies to argue on the one hand that they have had an appropriate concern for the safety of their products and on the other that they cannot provide test results showing the level of toxicants, carcinogens and addictive substances in their products. Tobacco product manufacturers have marketed their products for years with total disregard for the safety of their customers. The Tobacco Control Act was designed to force a change in this unacceptably dangerous practice and it is by no means unreasonable for FDA to require that such testing be done and full reporting required as a condition of any finding that a product be found substantially equivalent to a predicate product. If those requirements mean that

¹⁶⁷ *Id.* at 48

¹⁶⁸ Comments of Lorillard Tobacco Company in 2010-FDA-D-0635 at 7 (February 4, 2011).

fewer deadly products are marketed or that products that had been marketed without such testing have to be removed from the market, such results are appropriate. Unless and until manufacturers have done such testing and reported their data, such products should not be on the market.

C. Alleged lack of validated methods of analysis.

Lorillard also argues that the analysis called for in the Draft Guidance would be of “limited scientific value” because many of the proposed constituents lack well-established validated, and sensitive methods of analysis to permit meaningful comparisons among different products.¹⁶⁹ However, FDA found, informed by expert guidance provided by a TPSAC subcommittee consisting of many of the most eminent experts in testing in the world, that test protocols did exist for all the components.¹⁷⁰ While the precision of the testing may vary from one constituent to another, such variations can be compensated for by increasing the number of replicates.

Moreover, in the context of testing to establish substantial equivalence, differences attributable to the use of different testing laboratories are not relevant since the same laboratory can be used to test both the predicate product and the new product. The methodology for the testing of both products can be made to be identical. Since the relevant comparison for regulatory purposes will only be between the two products—and not with regard to a wide range of products of other manufacturers—meaningful comparisons of the test data should be possible.

Once again the industry proposals ignore the fact that the industry bears the burden of proof.

D. Alleged inconsistencies in reporting requirements between Section 904 and 905(j).

Lorillard and Commonwealth also object to alleged inconsistencies between the reporting requirements under section 904 and those under section 905(j).¹⁷¹ Specifically, Lorillard states

¹⁶⁹ *Id* at 7.

¹⁷⁰ 76 F.R. 50227 (August 12, 2011), Docket No. FDA-2011-N-0271.

¹⁷¹ Comments of Lorillard Tobacco Company in 2010-FDA-D-0635 at 7-8 (February 4, 2011); Comments of Commonwealth Brands, Inc., et al., in 2010-FDA-D-0635 at 7, 12-13 (March 3, 2011).

that reporting under section 904 does not require any breakdown of “complex purchased ingredients” where the ingredient is not made to the manufacturer’s specifications.¹⁷² However, the purposes of reporting under section 904 differ from those of reporting under section 905(j). While reporting under section 904 merely provides the agency with information, the purpose of reporting under section 905(j) is to provide a basis for regulatory decisions as to which products manufacturers will be permitted to market. The consequences of decisions made on the basis of information provided under section 905(j) are real and profound. Requiring more detailed information to support such significant regulatory decisions is entirely understandable. In the absence of such requirements, the public could be exposed to substantial increases in the level of toxicants, carcinogens, and addictive substances without regulatory oversight. Constituents are no less toxic, carcinogenic, or addictive because they are contained in complex ingredient mixtures purchased by manufacturers. Consequently, the requirement to test, analyze and report on the levels of such substances is entirely reasonable.

E. Proprietary blends and additives purchased from third parties.

Commonwealth argues that many complex ingredients are proprietary blends.¹⁷³ However, the proprietary nature of such blends presents no obstacle to the testing of the ultimate tobacco product that incorporates such a blend. The effect of such blends on the ultimate product will be reflected in the test results. It is the responsibility of the manufacturers to know what is in its products and to know the health impact of its products. The manufacturers’ responsibility is not diminished by making the product more complex.

Commonwealth and Lorillard also argue that manufacturers may use complex ingredients purchased from multiple suppliers interchangeably.¹⁷⁴ In order to obtain designation of a product as substantially equivalent, a manufacturer should be able to demonstrate that the smoke constituents of cigarettes using all such complex ingredients meet the regulatory standard. If different blends of complex ingredients purchased from third parties yield higher levels of toxicants, carcinogens, or addictive substances than those in the predicate product, manufacturers

¹⁷² Comments of Lorillard Tobacco Company in 2010-FDA-D-0635 at 8 (February 4, 2011).

¹⁷³ Comments of Commonwealth Brands, Inc., et al., in 2010-FDA-D-0635 at 13 (March 3, 2011).

¹⁷⁴ Comments of Lorillard Tobacco Company in 2010-FDA-D-0635 at 10 (February 4, 2011); Comments of Commonwealth Brands, Inc., et al., in 2010-FDA-D-0635 at 13 (March 3, 2011).

may have to alter their purchasing practices to conform to the regulatory requirement. Tobacco product manufacturers can avoid this difficulty by supplying test results for their products using the full range of ingredients purchased from third party suppliers.

F. Insufficiency of samples for testing

Products as to which insufficient samples exist to permit adequate testing cannot be predicate products. Philip Morris argues that there may be numerous instances in which a new product cannot be shown to be substantially equivalent to a predicate product because there are insufficient samples of the predicate product to permit testing that would establish the level of harmful and potentially harmful constituents.¹⁷⁵ The short answer to this assertion is that if insufficient samples exist to permit the required product testing the new product cannot be demonstrated to be substantially equivalent to the predicate product. Consumers should not be placed at risk of increased exposure to harmful or potentially harmful constituents or increased risk of tobacco-related disease simply because a manufacturer lacks the ability to demonstrate that its new product would not create such risks. If this means that the new product must meet the new product requirements of section 910 in order to be marketed, such a result is appropriate.

V. Changes in the Product to Ensure Consistency

Several manufacturers argue that changes in tobacco products made in order to ensure consistency of the product should not, by themselves, preclude classification of a product as substantially equivalent to a predicate product. Manufacturers argue that tobacco products are inherently variable because tobacco is an agricultural product the components of which can vary from time to time.¹⁷⁶ Manufacturers argue that, in order to ensure that a brand presents consistent taste and perception qualities to consumers, it may be necessary to (1) alter the blend of various tobacco components; (2) alter the level of additives to compensate for changes in taste or perception that would otherwise result; (3) alter the product design (such as changing ventilation holes in the cigarette). Manufacturers argue that the need for making such changes

¹⁷⁵ Comments of Philip Morris USA, Inc. and US Smokeless LLC in FDA-2010-D-0635 at 7-8 (March 22, 2011).

¹⁷⁶ Comments of Philip Morris USA, Inc. and US Smokeless LLC in FDA-2010-D-0635 at 3. Comments of Philip Morris USA, Inc. and US Smokeless LLC in FDA-2010-D-0646 at 7. Comments of R.J. Reynolds Tobacco Company in FDA-2010-D-0635 at 22-23; Comments of R.J. Reynolds Tobacco Company in FDA-2010-D-0646 at 7; Comments of Liggett Group LLC in FDA-2010-D-0635 at 13. (June 10, 2011).

arises frequently and that the requirement that a substantial equivalence report be made and an application granted before such changes can be made makes implementation of such changes in the product impractical.

A. Changes in tobacco blends

FDA addresses tobacco blending changes “made to address variation in tobacco growing conditions” in Question 8 of its Frequently Asked Questions (FDA-2011-D-0147). FDA states that it “does not intend to enforce the requirements of [the substantial equivalence application process] for tobacco blending changes required to address the *natural* variation of tobacco (i.e., tobacco blending changes due to variation in growing conditions) in order to maintain a consistent product.” It notes, however, that “tobacco blending changes that are intended to alter the chemical or perception properties of the new product (e.g., nicotine level, pH, smoothness, harshness, etc.) compared to the predicate should be reported in a premarket application under section 910 and 905(j). . . .” and urges the companies to discuss questions regarding blending changes with the agency.

The policy announced by FDA does not apply if the tobacco blending changes “are intended to alter the chemical or perception properties of the new product (e.g., nicotine level, pH, smoothness, harshness, etc.) compared to the predicate product.”¹⁷⁷ In our prior comments, we urged FDA to strengthen this condition by making it clear that the policy would not apply if the tobacco blending changes had either the intention *or the effect* of altering the chemical or perception properties of the new product.¹⁷⁸ We continue to urge FDA to do so. Particularly in light of this industry’s historic practices of fraud and deception, we believe it is unwise for FDA to permit a company to market a product merely on the basis of a stated “intention.” FDA’s regulations should focus on effect, not on intention. We have a serious and factually based concern that tobacco product manufacturers will abuse the leeway FDA’s announced policy would provide them to introduce a range of changed products that are more addictive or increase the disease risk of consumers.

¹⁷⁷ FDA Frequently Asked Questions, Docket No. FDA-2011-D-0147 at 7.

¹⁷⁸ Tab A (Comments of American Cancer Society Cancer Action Network, *et al.* in FDA-2010-D-0635, March 22, 2011) at 7-8.

If FDA nevertheless chooses to apply this policy, it is essential that it require any tobacco product manufacturer taking advantage of this provision to provide a full and timely report to FDA of any instances in which such changes are implemented, to undertake and report to FDA the results of tests demonstrating that the changes have not resulted in changes in the nicotine delivery or the pH of the smoke or increased the level of any harmful or potentially harmful constituent and to discontinue the blending change if such results are observed.

It is understandable that tobacco product manufacturers wish to have a brand maintain a consistent taste. Nevertheless, this interest should not be permitted to override the fundamental objective of protecting the public health. We believe that such changes do in fact “raise different questions of public health” as that term is used in Section 910 and that Congress did not intend for such changes to be left to the discretion of tobacco product manufacturers. Nothing in the Tobacco Control Act indicates that Congress intended that changes required to maintain a consistent taste should be permitted at the cost of increasing the exposure of consumers to harmful or potentially harmful constituents.

B. Changes in additives to maintain consistency

Several manufacturers argue that maintaining a consistent taste for a brand may require changing the level of additives to compensate for changes in the tobacco blend itself. Nothing in FDA’s draft guidance or its answers to frequently asked questions indicates that the leeway permitted with regard to changes in tobacco blend extends to changes in the level of additives.¹⁷⁹ It may be possible for manufacturers to demonstrate in advance of any such changes that a given range of changes in one or more additives would not violate the public health standard for a particular brand. No such exemption should be provided, however, except on the basis of tests performed in advance of such changes and with the prior grant of authority from FDA.

¹⁷⁹ FDA Guidance for Industry and FDA Staff Section 905(j) Reports: Demonstrating Substantial Equivalence for Tobacco Products (January 5, 2011) FDA Draft Guidance for Industry and FDA Staff Demonstrating the Substantial Equivalence of a New Tobacco Product: Responses to Frequently Asked Questions, Docket No. FDA-2011-D-0147 (September 2011).

C. Changes in product design to maintain consistency

Several manufacturers argue that changes in product design have historically been used in order to maintain consistency of a brand.¹⁸⁰ They suggest, for example, that changes in the spacing of ventilation holes can be used to affect the taste of the cigarette.¹⁸¹ Such changes, however, have in the recent past resulted in changes in smoking topography that have been demonstrated to cause increased exposure to toxic and carcinogenic constituents. The sad history of the promotion of “light” cigarettes shows how product design changes can dramatically increase the disease risk of cigarettes. Given this history, it would be a mistake for FDA to permit tobacco manufacturers to make design changes merely because they are alleged to be intended to maintain the taste consistency of cigarettes. Even changes that do in fact maintain the taste consistency of cigarettes can at the same time increase the disease risk of consumers.

D. Summary of arguments on modifications to preserve consistency

In sum, tobacco product manufacturers maintain that (1) tobacco products change because the constituents in tobacco itself change as a result of changes in growing conditions; (2) historically, manufacturers have attempted to maintain consistency of taste for given brands by (i) altering the blend of tobacco in a brand; (ii) changing the level of additives; and (iii) changing the product design. Historically, tobacco product manufacturers have had complete discretion to make whatever changes in their products they wished without informing the public or any regulatory agency. In fact, no one outside the company was in a position to know that any such changes were being made. Tobacco product manufacturers abused this discretion. They created products that caused the largest preventable public health problem in the United States and the world. They designed products to maximize their addictive potential. They designed products without regard to their toxicity or carcinogenicity. Although they conducted meticulous product testing to determine how their products should taste in order to maximize their market potential, they disregarded the impact of product changes on the death and disease they would

¹⁸⁰ Comments of Philip Morris USA, Inc. and US Smokeless LLC in FDA-2010-D-0646 at 7 (March 22, 2011). Comments of R.J. Reynolds Tobacco Company in FDA-2010-D-0635 at 22-23. Comments of Lorillard Inc. in Docket No. FDA-2010-D-0646 at 5 (March 22, 2011).

¹⁸¹ Comments of Philip Morris USA, Inc. and US Smokeless LLC in FDA-2010-D-0646 at 8 (March 22, 2011)

cause. They misrepresented the health consequences of their products and they suppressed research findings that would have revealed how dangerous their products were.

The Tobacco Control Act was designed not to preserve the status quo but to change it. The tobacco companies argue strenuously that the regulatory structure created by the Tobacco Control Act will require significant changes in the way they manufacture cigarettes and make it more difficult for them to manufacture brands that have a consistent taste. This may well be the case. The Tobacco Control Act did not guarantee cigarette manufacturers the right to continue doing what they have done merely because it is convenient and profitable to do so. Given the way tobacco product manufacturers have used changes in additives and product design to make their products more addictive and more dangerous, it would make no sense to create a regulatory structure in which they could continue to make such changes without first demonstrating their likely effect.

VI. Relationship to Regulations for Minor Modifications

Lorillard criticizes FDA for failing to propose exempt categories in the draft regulations promulgated for minor modifications and argues that FDA's failure to do so means that FDA should provide greater flexibility in its review of substantial equivalence filings.¹⁸² Lorillard fails to take account of the difficulties faced by FDA in initiating a new regulatory program covering a set of products that had previously never been regulated and that constitutes the nation's largest preventable cause of death. For many decades tobacco companies have been free to introduce new products into the marketplace with no regulatory constraint. The major tobacco companies developed an extremely sophisticated understanding of the preferences of its market and used this understanding to introduce thousands of new tobacco products designed to appeal to these preferences. In developing and marketing these products, tobacco companies considered only their marketing opportunities; they paid no attention to the public health consequences of their actions. In the tobacco industry, innovation has been devoted solely to maximizing industry profit with no concern for public health and the result has been the public health disaster that FDA has been designated to address. The Tobacco Control Act directs FDA to make public health considerations a decisive factor in determining whether new tobacco products can be

¹⁸² Comments of Lorillard Tobacco Company in FDA-N-0646 at 2, 4-5 (March 22, 2011).

marketed. This policy represents a sharp break with past practice. Lorillard and the other major tobacco companies criticize FDA's proposed guidance for substantial equivalence and its proposed rule for minor modifications because they will require a departure from past practice. However, a departure from past practice is precisely what is required by the Tobacco Control Act.

FDA is keenly aware of the importance of its regulatory responsibilities with regard to tobacco products. It is also aware of the consequences of its early decisions regarding substantial equivalence and modifications to tobacco products. Once FDA deems a new product substantially equivalent, the new product itself becomes a potential predicate product. Moreover, FDA's action sets a precedent that may have profound consequences for the millions of Americans who use tobacco products and many millions more who are potential users. Under these circumstances, FDA should move cautiously before it takes action on substantial equivalence applications and the designation of categories of changes that may qualify as minor modifications. An erroneous decision can have huge public health consequences.

In addition, FDA is dealing with an industry with an unparalleled record of duplicity. In light of this industry's history of deceit, no claim that it makes is entitled to a presumption of truth. This unfortunate but undeniable fact makes FDA's job even harder.

Delays in the marketing of new tobacco products are a small price to pay for a decision-making process that can better protect public health. FDA is correct to withhold designation of categorical changes in tobacco products as "minor modifications" or designation of new products as substantially equivalent to predicate products until it has a high degree of confidence that the decisions it is making are appropriate for the protection of the public health. The dangers of a policy that is too permissive toward the introduction of new and potentially more lethal products far outweigh those of a policy that is restrictive.

Philip Morris makes several arguments for the designation of certain product changes as "minor modifications." It argues that reduction or elimination of an additive should be categorically exempt from the substantial equivalence requirements.¹⁸³ It also argues that a

¹⁸³ Comments of Philip Morris, USA Inc. and US Smokeless LLC in FDA-2010-D-0646 at 6 (March 22, 2011).

tightening of the range for an additive to a point within the range that existed in the predicate product should also be categorically exempt and that a change in a “processing aid” should not be considered a modification.¹⁸⁴ With sufficient experience, it may be possible for FDA to develop standards for classification of some types of changes as “minor modifications.” FDA is properly concerned, however, that issuance of such a classification might result in unintentionally exposing consumers to unnecessary risks. If and when FDA does adopt categories of “minor modification,” it should include provisions for checking the product to determine whether it properly falls within the defined category.

VII. FDA should make more information available to the public about applications for substantial equivalence.

As these comments make clear, establishment of FDA’s policy regarding substantial equivalence is a matter of high public importance. Ironically, however, citizens interested in understanding how that policy is evolving have virtually no way to know how FDA is processing the 3,500 applications it has before it or even the products covered by any of the applications. Accordingly, it is impossible for anyone except the tobacco product manufacturers themselves to have a dialogue with FDA about what should be required. Thus, FDA receives extensive input from tobacco product manufacturers and conducts a dialogue with them regarding their applications, but citizens who are not tobacco product manufacturers with applications pending have no insight into the process. Although FDA has issued a guidance with regard to substantial equivalence and responses to frequently asked questions, as well as conducting two webinars, the information provided was insufficient to understand what criteria FDA is considering as the basis for decision on such applications. Lacking such basic information, citizens cannot participate in any kind of informed dialogue. Moreover, by treating the process of considering substantial equivalence applications as a closed process, FDA is depriving itself of the advice of those with real expertise on relevant scientific issues. FDA’s decision-making process would benefit greatly from broadening the sources of information it draws upon and from creating a public dialogue about the issues under consideration. In addition, FDA should establish a means of informing the public about the disposition of substantial equivalence applications, including publication—in redacted form if necessary—of decisions denying such applications. Only by

¹⁸⁴ *Id.* at 10-11.

fully explaining its reasoning process on the public record can FDA communicate to the public what standards it is applying. Such open communication would not only improve the quality of FDA's decisions, but it would also permit the public to understand the steps FDA is taking to discharge its responsibilities under the Tobacco Control Act to protect the public health.