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Division of Dockets Management (HFA305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. 2011-D-0212

To Whom It May Concern:

The undersigned organizations submit these comments on the Draft Guidance distributed by the FDA in Docket No. FDA-2011-D-0212 regarding Applications for Premarket Review of New Tobacco Products.

Section 910 of the Family Smoking Prevention and Tobacco Control Act (“FSPTCA”), which governs applications for pre-market orders of the FDA for the marketing of new tobacco products, requires FDA to make determinations pursuant to a regulatory standard never before applied to tobacco products. Moreover, the statutory standard also differs significantly from the standard applied by FDA in the regulation of other products. Congress created this standard because many regulatory considerations applicable to tobacco products differ from those applicable to other products. The draft guidance FDA has issued represents an effort to designate the information FDA will require in applying this standard. This guidance provides considerable specificity about such information and demonstrates a serious effort by FDA to create a workable foundation for the application of the new regulatory standard. These comments are designed to provide additional suggestions to help ensure that the statutory requirements are fulfilled.

Regulation of New Tobacco Products under the FSPTCA

With certain exceptions, the statute permits manufacturers to continue to market the same products they were marketing as of February 15, 2007 (i.e., “existing products”) provided

they are in compliance with any product standards FDA may establish pursuant to Section 907.¹ However, the statute prohibits manufacturers from marketing tobacco products that are “new” unless they comply with additional regulatory requirements.

The statute defines a new tobacco product as

“any tobacco product (including those in test markets) that was not commercially marketed in the United States as of February 15, 2007; or any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of a tobacco product where the modified product was commercially marketed in the United States after February 15, 2007.”

Section 910(a)(1).

It is important to note that “new products” include all products modified after February 15, 2007.

Establishment of a policy regarding applications for premarket review of new tobacco products is part of the broader issue of FDA’s policy with regard to the regulation of new tobacco products. The general rule is that new tobacco products may not be marketed unless and until FDA has granted an order permitting them to be marketed. The statute creates three alternative methods by which a manufacturer can meet the regulatory requirements to market a new tobacco product: (1) in the case of products introduced after March 22, 2011, the issuance of an order by FDA pursuant to an application submitted prior to marketing, that the new tobacco product is “substantially equivalent” to a product marketed on February 15, 2007 (for products introduced after February 15, 2007 but before March 22, 2011 for which an application was filed by March 22, 2011, the product may remain on the market in the absence of an order issued by FDA); (2) compliance with regulations establishing that certain modifications are “minor modifications” of a product marketed on February 15, 2007; or (3) the issuance of an order by FDA pursuant to an application submitted prior to marketing that permits a new product to be marketed. Of the three paths to market, an application seeking a marketing authorization order under section 910(c)(1)(A)(i) is the pathway that requires compliance with the most rigorous set of criteria. Although there have been several thousand applications for new products to be designated “substantially equivalent,” there have been no applications for new product authorizations. This pattern raises concern that the industry is interpreting these sections in a way that seeks to bypass the more rigorous scrutiny of Section 910 in situations where that section should apply.

¹ The statute prohibits the marketing of certain classes of tobacco products, whether or not they were marketed on February 15, 2007. Examples of such products are flavored cigarettes and cigarettes labeled as “light” or “mild.” FDA has promulgated regulations to implement these prohibitions. As noted in the text, Section 907 gives FDA authority to issue product standards that could also result in prohibiting the marketing of certain classes of cigarettes that were marketed on February 15, 2007.

Because the new product application procedures under Section 910 are part of a larger structure for regulating all new products, it is important to consider them in the context of the standards for substantial equivalence and minor modifications. The undersigned organizations have submitted extensive comments on the establishment of appropriate standards for substantial equivalence and minor modifications. We attach those comments hereto with the intention that these comments be read in conjunction with them to establish a comprehensive structure for the regulation of new products.

The fundamental principle underlying the FSPTCA's regulatory structure for new products is that such products should be evaluated by FDA on a pre-market basis and should not be marketed in the absence of an FDA order. Such pre-market review has traditionally been applied to drugs and medical devices. However, significantly, the standard applicable to FDA's review of new tobacco product applications is different from the standard applied in the review of drugs and medical devices and requires consideration of evidence of a different nature.

I. In the absence of regulatory requirements, the introduction of new tobacco products greatly increased death and disease.

Practice before the enactment of the FSPTCA left the public health completely unprotected. The introduction of new products enabled the industry to make changes to their products without regard to the impact of such changes on the health of tobacco users, to increase the addiction risk of products with no regard for the death and disease that was the inevitable result, and to enhance the appeal and ease of use of their products to and by youth and other non-tobacco users.

Prior to the enactment of the FSPTCA there were no federal regulatory restrictions on the ability of manufacturers to introduce new tobacco products. The absence of any regulatory criterion also meant that there was no requirement that the tobacco companies study the impact of product or design changes or alterations on disease risk, or abuse liability or report what they did know. Nor was there any requirement that tobacco companies consider the impact of such changes on youth on or on the ability of tobacco users to quit. In the absence of regulatory standards, tobacco manufacturers made product changes that increased the levels of known carcinogens over time and increased the intensity and speed of delivery of nicotine.² In addition, these changes made it more attractive for non-tobacco users to experiment with cigarettes and harder for current tobacco users to quit.

² Burns, DM, Anderson, CM, and Gray, N., "Has the Lung Cancer Risk from Smoking Increased Over the Last fifty Years?," *Cancer Causes Control*, 22: 389-397, March 2011; Burns, DM, Anderson, CM, and Gray, N., "Do changes in cigarette design influence the rise in adenocarcinoma of the lung?" *Cancer Causes Control*, 22:13-22, January, 2011; Bates, C, Jarvis, M, & Connolly, G, *Tobacco additives: Cigarette engineering and nicotine addiction*, ASH UK, July 14, 1999, http://newash.org.uk/files/documents/ASH_623.pdf; Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), *Addictiveness and Attractiveness of Tobacco Additives*, 2010 http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_031.pdf

At no time were tobacco manufacturers required to tell the government or the public about these changes or to conduct tests so that the government or the public would be able to evaluate the impact of these changes. At no time were there any restrictions on changes that directly increased the number of people who die from tobacco use or that presented barriers to efforts to reduce the number of people who die from tobacco use. In addition, for many decades the tobacco industry used the introduction of new products to deceive the public into falsely believing that certain new products posed a lesser danger of death and disease without any scientific evidence to support that belief.³

A review of what is known about product changes over the last several decades and of tobacco industry documents provides no evidence that tobacco companies gave serious consideration to the adverse impact of product changes on public health when they decided to market new products. Rather, the evidence indicates that the object of such decisions was simply to expand the sale of tobacco products regardless of the adverse impact on public health and that tobacco manufacturers deliberately deceived the public about the known health risks. *U.S. v. Philip Morris, supra*.

The result of the unregulated introduction of new products was to magnify the public health threat in numerous respects. First, the introduction of new or modified products brought more consumers into the market. Many new products were designed to appeal to targeted segments of the population.⁴ Products were made more appealing by design changes in the product that subtly affected its taste by making the smoke seem smoother and cooler.⁵ The proliferation of products made it possible for manufacturers to design and market a range of products that would appeal to a broader range of consumers and tastes.⁶ It is important to note that even when such changes neither made cigarettes more toxic nor more addictive they nevertheless were harmful to the public health when they attracted people to smoking who

³ National Cancer Institute, *Risks Associated with Smoking Cigarettes with Low Machine-Yields of Tar and Nicotine; Report of the NCI Expert Committee*. National Institutes of Health. National Cancer Institute. Smoking and Tobacco Control Monograph 13, 2001 <http://cancercontrol.cancer.gov/tcrb/monographs/13/>. *U.S. v. Philip Morris USA, Inc., et al.*, 449 F. Supp.2d 1 at 740, 877-888 (D.D.C. 2006), aff'd in relevant part, 566 F.3d 1095 (D.C. Cir. 2009), cert. denied, 130 S. Ct. 3501 (2010), Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), *Addictiveness and Attractiveness of Tobacco Additives*, 2010.

⁴ National Cancer Institute, *Risks Associated with Smoking Cigarettes with Low Machine-Yields of Tar and Nicotine; Report of the NCI Expert Committee*. National Institutes of Health. National Cancer Institute. Smoking and Tobacco Control Monograph 13, 2001. See also, Kreslake, JM, et. Al., "Tobacco industry Control of Menthol in Cigarettes and Targeting of Adolescents and Young Adults," *American Journal of Public Health*, Vol. 98 No. 9, September, 2008; U.S. Department of Health and Human Services (HHS), *Women and Smoking: A Report of the Surgeon General*, Washington, DC: HHS, Public Health Service, Office of the Surgeon General, 2001, http://www.cdc.gov/tobacco/data_statistics/sgsr/index.htm

⁵ Kreslake, JM, et. Al., "Tobacco industry Control of Menthol in Cigarettes and Targeting of Adolescents and Young Adults," *American Journal of Public Health*, Vol. 98 No. 9, September, 2008; National Cancer Institute, *Risks Associated with Smoking Cigarettes with Low Machine-Yields of Tar and Nicotine; Report of the NCI Expert Committee*. National Institutes of Health. National Cancer Institute. Smoking and Tobacco Control Monograph 13, 2001; Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), *Addictiveness and Attractiveness of Tobacco Additives*, 2010.

⁶ National Cancer Institute, *Risks Associated with Smoking Cigarettes with Low Machine-Yields of Tar and Nicotine; Report of the NCI Expert Committee*. National Institutes of Health. National Cancer Institute. Smoking and Tobacco Control Monograph 13, 2001. NCI Monograph 13 documents how cigarette manufacturers integrated cigarette design changes with marketing to achieve this goal. See also, Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), *Addictiveness and Attractiveness of Tobacco Additives*, 2010.

otherwise would not have smoked. One important lesson to be drawn from this experience is that a new product that is more attractive to a group of potential smokers than existing products constitutes a danger to the public health even if that new product is neither more addictive nor more toxic than any existing product.⁷

Second, the unregulated introduction of new or modified products made it less likely that existing smokers would successfully quit. Quit attempts might be discouraged either because a new or modified product might have a smooth enough taste to lead a smoker who otherwise would quit to continue smoking or to falsely conclude that smoother meant less dangerous or because a new or modified product delivered an addictive substance more effectively or in greater quantity than existing products.⁸ For any of these reasons, a smoker who might otherwise have quit would be influenced to continue smoking instead. The addictiveness of a product could be increased whether or not the product actually contained a greater amount of an addictive substance. Long before it was known to the public, tobacco companies knew that the form in which nicotine is delivered can affect the speed with which it is absorbed, the amount absorbed, and the location in the body it impacted.⁹ They also knew that a cigarette's addictiveness could be increased by manipulating the pH level of the smoke.¹⁰

Third, the unregulated introduction of new or modified products made it possible to introduce substances or smoke constituents that increased the amount of toxins delivered to smokers. For example, design changes in cigarettes over the course of many years resulted in increasing the amount of tobacco specific nitrosamines (TSNA's) delivered to the lung. Dr. David Burns conducted two studies that provide powerful evidence that the increase in the level of TSNA's in American cigarettes may be accountable for his finding that the modern smoker is

⁷ For example, the introduction of sugar or chocolate as an ingredient in cigarettes masks the harshness of the smoke and leads a larger number of individuals to become smokers even if the flavor is not present at levels at which it can be detected as a flavoring. Bates, C, Jarvis, M, & Connolly, G, *Tobacco additives: Cigarette engineering and nicotine addiction*, ASH UK, July 14, 1999, http://newash.org.uk/files/documents/ASH_623.pdf.

⁸ Shiffman, S., et. Al., "Smokers' beliefs about "Light" and "Ultra Light" Cigarettes," *Tobacco Control*; 10 (Suppl D): i17-i23, 2001; Giovino, G. et al., "Attitudes, Knowledge, and Beliefs About Low-yield Cigarettes Among Adolescents and Adults," in National Institutes of Health, National Cancer Institute, *The FTC Cigarette Test Method for Determining Tar, Nicotine, and Carbon Monoxide Yields of U.S. Cigarettes; Report of the NCI Expert Committee, Smoking and Tobacco Control Monograph 7*; Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), *Addictiveness and Attractiveness of Tobacco Additives*, 2010.

⁹ Bates, C, Jarvis, M, and Connolly, G, *Tobacco additives: Cigarette engineering and nicotine addiction*, ASH UK, July 14, 1999. See also, *U.S. V. Philip Morris USA, Inc., et al.*, No. 99-CV-02496GK (U.S. Dist. Ct., D.C.), Final Opinion, pg. 601, August 17, 2006, <http://www.tobaccofreekids.org/reports/doj/FinalOpinion.pdf>; Riehl T, et al., Project SHIP review of progress November 5-6 1984 BAT, November 12th, 1984, Minn Trial Exhibit 10752; Anderson HD. Potassium carbonate Memo to RP Dobson, BAT, August 7th 1964, Minn Trial Exhibit 10356; *U.S. V. Philip Morris USA, Inc., et al.*, No. 99-CV-02496GK (U.S. Dist. Ct., D.C.), Final Opinion, pg. 517-519, August 17, 2006.

¹⁰ Bates, C, Jarvis, M, and Connolly, G, *Tobacco additives: Cigarette engineering and nicotine addiction*, ASH UK, July 14, 1999. See also, Liggett, January 29th 1974, Development of a Cigarette with an Increased Smoke pH ; Colby FG. Cigarette concept to assure RJR a larger segment of the youth market. December 4th 1973, Minn Trial Exhibit 12464; RJR 1976, McKenzie JL. Product characterization definitions and implications. Minn Trail Exhibit 12270.

at an even greater risk of lung cancer than smokers in the mid-1960s, a remarkable and disturbing conclusion.¹¹

The fundamental point is that product design has an important effect on the number of people who smoke, the degree to which they become addicted, the quantity of toxic substances to which they are exposed, and the number of people who die from smoking. To permit changes in product design without regulation is to leave consumers completely at the mercy of the tobacco companies.

In addition, many new products were marketed in ways that conveyed a false sense of safety and created the illusion that they were somehow less dangerous; others expanded the harm caused by their enhanced appeal to a more diverse consumer base.¹² New products also enabled tobacco companies to cultivate distinct images for different products with which adolescents identified.¹³ Often the combination of product design and marketing worked together to mislead consumers. For example, as design changes made the smoke of many cigarettes smoother and the tobacco industry touted the smoothness, many consumers interpreted both the taste and the advertising to mean that the cigarette was safer.¹⁴ New products encouraged smoking initiation, facilitated addiction, discouraged cessation, and caused the premature death of millions of Americans. Congress had ample reason to impose regulatory restrictions on the introduction of new tobacco products.

II. Application of the standard for pre-market review of new products.

A. The statutory standard for new products is a rigorous one.

The FSPTCA's approach to the regulation of new tobacco products represents a departure from the way the tobacco industry operated previously. The FSPTCA is not designed to permit the tobacco companies to continue to introduce new products without regard to the death and

¹¹ Burns, DM, Anderson, CM, and Gray, N., "Has the Lung Cancer Risk from Smoking Increased Over the Last fifty Years?," *Cancer Causes Control*, 22: 389-397, March 2011; Burns, DM, Anderson, CM, and Gray, N., "Do changes in cigarette design influence the rise in adenocarcinoma of the lung?" *Cancer Causes Control*, 22:13-22, January, 2011.

¹² National Cancer Institute, *Risks Associated with Smoking Cigarettes with Low Machine-Yields of Tar and Nicotine; Report of the NCI Expert Committee*. National Institutes of Health. National Cancer Institute. Smoking and Tobacco Control Monograph 13, 2001; Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), Addictiveness and Attractiveness of Tobacco Additives, 2010; *U.S. V. Philip Morris USA, Inc., et al.*, No. 99-CV-02496GK (U.S. Dist. Ct., D.C.), Final Opinion, pg. 877-878, August 17, 2006.

¹³ Pierce, JP, et al. Camel No. 9 Cigarette-Marketing Campaign Targeted Young Teenage Girls. *Pediatrics* 125(4):619-626, April 2010; Felberbaum, M. State AGs ask RJ Reynolds to stop Camel cigarette 'Break Free Adventure' marketing campaign. *Associated Press*. December 1, 2010

¹⁴ Wayne, GF, & Connolly, GN, "How Cigarette Design Can Affect Youth Initiation into Smoking: Camel Cigarettes, 1983-1993," *Tobacco Control* 11:i32 - i39, March 2002. Bates, C, Jarvis, M, & Connolly, G, *Tobacco additives: Cigarette engineering and nicotine addiction*, ASH UK, July 14, 1999; Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), Addictiveness and Attractiveness of Tobacco Additives, 2010.

disease caused by those products or the number of people who will be adversely affected. Rather, it is designed to make fundamental changes in order to protect the public health.

The FSPTCA gave FDA the authority to regulate tobacco products in order to protect the public health by regulating existing products and, for the first time, establishing procedures and criteria based on protection of public health that have to be met before new products can be marketed.

Appropriately, the statute created a rigorous new standard that new products would have to meet in order to be put on the market and unambiguously placed the burden on the industry to prove that the standard had been met before new products can be marketed.

Under the new standard, a new product may not be introduced unless the FDA determines that the introduction of the new product is “appropriate for the protection of the public health [considering] the risks and benefits to the population as a whole” and taking into account the increased or decreased likelihood that non-users will start using such products and the increased or decreased likelihood that existing users will quit.

These latter two requirements cannot be totally satisfied by an analysis of the physical aspects of the product or its smoke constituents or the physical effects of any substance in the product or its smoke constituents on users of the product. While this type of analysis is necessary, it is not sufficient. Rather, these requirements can be satisfied only after an analysis of evidence presented on the likely consumer response to the product, including its packaging. A product that is likely to lead to an increase in smoking initiation cannot satisfy the public health standard even if its physical effects on users or non-users are no different from those of other tobacco products.

As we have noted, the burden of establishing each of these elements is placed on the manufacturer. FDA is directed to deny the application if “there is a lack of a showing that permitting such tobacco product to be marketed would be appropriate for the protection of the public health.”

The standard FDA is directed to apply is different from the standard it applies when it considers whether to permit a new drug on the market. A new drug is permitted to be marketed if the sponsor establishes that it is “safe and effective.” But new drugs have a therapeutic purpose. Although they may pose risks, they also convey benefits. By contrast, no tobacco product is safe and no tobacco product has been found to confer a therapeutic benefit. Therefore, whenever FDA reviews a new tobacco product application it is considering a product that kills when used exactly as intended, for which there is no safe level of exposure, and which confers no therapeutic benefit.

The statute directs FDA to consider more than the toxicity or addictiveness of the new product. When it established the public health standard, Congress directed FDA to consider

whether the new product would increase or decrease initiation of smoking and whether it would increase or decrease cessation. The very nature of this inquiry requires FDA to determine how widely the product is likely to be used in the marketplace and by what groups. Because tobacco products are lethal, a product that is no more toxic or addictive than existing products will fail to meet the standard if the manufacturer is unable to demonstrate that its introduction is not likely to increase initiation or decrease cessation.

B. The standard reflects a recognition that product changes can substantially increase risks to the public health.

Changes in tobacco products can substantially increase risks to the public health even if such changes do not directly increase the quantity of toxins in a product or increase the quantity of substances that are themselves addictive. Such changes can take several forms, including but not limited to the following.

*Increasing the absorption of nicotine.*¹⁵ Most smokers inhale cigarette smoke deeply into the lung. Nicotine absorption in the lung has a high potential to cause dependence because of the rapid delivery of small doses of nicotine to the brain.¹⁶ Modifying pH levels changes smoke chemistry in ways that can enhance nicotine absorption into the bloodstream as well as nicotine activation of nerve endings in the oral cavity that transmit signals to the brain.¹⁷ Nicotine exists in two forms, bound and unbound (“free”). Increasing the pH level increases the proportion of free nicotine, which is more physiologically active than bound forms and able to cross biological membranes into the bloodstream with greater ease.¹⁸ Ammonia compounds and other alkaline additives such as diammonium phosphate and urea are used in cigarette manufacturing to manipulate pH level.¹⁹ The use of such substances therefore has the effect of increasing the addictiveness of the product, thereby increasing the likelihood that young people experimenting with cigarettes will become addicted and reducing the likelihood that existing users will quit.

Similarly, sugar and polysaccharides are commonly added to tobacco products. By themselves, these additives are not addictive; however, when burned they form numerous

¹⁵ This paragraph and the following paragraph are taken from the Framework Convention Alliance briefing paper on the addictiveness of tobacco products, prepared for the World Health Organization FCTC Article 9 and 10 Working Group meeting, January 2012.

¹⁶ World Health Organization, *The Scientific Basis of Tobacco Product Regulation*, Report of a WHO Study Group, WHO Technical Report Series 945, 2007; Bates, C, Jarvis, M, and Connolly, G, *Tobacco additives: Cigarette engineering and nicotine addiction*, ASH UK, July 14, 1999.

¹⁷ World Health Organization, *The Scientific Basis of Tobacco Product Regulation*, Report of a WHO Study Group, WHO Technical Report Series 945, 2007; Bates, C, Jarvis, M, and Connolly, G, *Tobacco additives: Cigarette engineering and nicotine addiction*, ASH UK, July 14, 1999; Megerdichian, C.L., et. al., “Internal tobacco industry research on olfactory and trigeminal nerve response to nicotine and other smoke components,” *Nicotine Tob. Res.* 9, 2007.

¹⁸ Bates, C, Jarvis, M, & Connolly, G, *Tobacco additives: Cigarette engineering and nicotine addiction*, ASH UK, July 14, 1999. See also, Anderson HD. Potassium carbonate Memo to RP Dobson, BAT, August 7th 1964, Minn Trial Exhibit 10356; RJR 1976, McKenzie JL. Product characterization definitions and implications. Minn Trail Exhibit 12270.

¹⁹ Bates, C, Jarvis, M, & Connolly, G, *Tobacco additives: Cigarette engineering and nicotine addiction*, ASH UK, July 14, 1999; Food and Drug Administration, 1996. Regulations restricting the sale and distribution of cigarettes and smokeless tobacco to protect children and adolescents, Final Rule. Federal Register 61, 44396–45318; Henningfield, J.E., et. al., “Reducing tobacco addiction through tobacco product regulation,” *Tobacco Control*, 13: 132-135, 2004.

aldehydes, such as formaldehyde and acetaldehyde. Acetaldehyde has been shown not only to have addictive potential in itself, but also has been shown to enhance the addictive potential of nicotine.²⁰

Enhancing the ease and attractiveness of tobacco use. Flavorings increase the palatability of cigarette smoke and, in the case of menthol, could facilitate deeper inhalation and higher nicotine dose due to their perceived cooling effects.²¹ Moreover, flavorings such as chocolate are frequently introduced at levels too low to be perceived as characterizing. There is evidence that the introduction of such substances helps to reduce the inherent harshness of tobacco smoke even when such substances are not present at levels sufficient to be perceived as flavors.²² The addition of such substances therefore increases the number of smokers, both by making smoking initiation more likely, by making it more likely that those experimenting with cigarettes would become regular smokers, and by making it less likely that regular users would attempt to quit. Changes in the levels of such substances would therefore “increase the risks to the population as a whole” within the meaning of section 910(c)(4).

Other design changes. Design changes in cigarettes can also increase the risks to the population as a whole even if they do not involve the introduction of new substances or smoke constituents. Cigarettes with higher levels of filter ventilation dilute the smoke inhaled by smokers and thus affect the way consumers smoke.²³ Design changes can increase initiation and make it more likely that those experimenting with cigarettes will become regular smokers. Such changes are frequently tailored to appeal to certain target groups or communities or to remove the barriers that led certain users and groups not to smoke or not to become regular smokers and thus may have a disproportionate public health impact in such communities.²⁴

²⁰ Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), Addictiveness and Attractiveness of Tobacco Additives, 2010 ; Bates, C, Jarvis, M, & Connolly, G, *Tobacco additives: Cigarette engineering and nicotine addiction*, ASH UK, July 14, 1999. World Health Organization, The Scientific Basis of Tobacco Product Regulation, Report of a WHO Study Group, WHO Technical Report Series 945, 2007. See also, DeNoble VJ, et. Al., Reinforcing activity of acetaldehyde [abstract]. Philip Morris.

²¹ Bates, C, Jarvis, M, & Connolly, G, *Tobacco additives: Cigarette engineering and nicotine addiction*, ASH UK, July 14, 1999. World Health Organization, The Scientific Basis of Tobacco Product Regulation, Report of a WHO Study Group, WHO Technical Report Series 945, 2007; <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/ucm247605.htm>.

²² World Health Organization, The Scientific Basis of Tobacco Product Regulation, Report of a WHO Study Group, WHO Technical Report Series 945, 2007. Bates, C, Jarvis, M, & Connolly, G, “Tobacco additives: Cigarette engineering and nicotine addiction,” ASH UK, July 14, 1999, See also, Wayne GF, Conolly GN, “How cigarette design can affect youth initiation into smoking: Camel cigarettes 1983-93,” *Tobacco Control*, 11 (Suppl 1), 2002. Cummings KM, et al, “Marketing to America’s youth: evidence from corporate documents,” *Tobacco Control*, 11 (Suppl 1), 2002; Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), Addictiveness and Attractiveness of Tobacco Additives, 2010.

²³ Bates, C, Jarvis, M, & Connolly, G, *Tobacco additives: Cigarette engineering and nicotine addiction*, ASH UK, July 14, 1999; Benowitz NL, Hall SM, Herning, RI et al., “Smokers of low-yield cigarettes do not consume less nicotine,” *New England Journal of Medicine*, 309: 139-42, 1983.

²⁴ Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), Addictiveness and Attractiveness of Tobacco Additives, 2010; Carpenter CM, Wayne GF, Connolly GN, “The role of sensory perception in the development and targeting of tobacco products,” *Addiction* 102:136-47, 2007.

III. Evidence required to meet the regulatory requirements for new tobacco products

The statute properly allows FDA to determine what specific evidence to consider, but at a minimum it should include evidence about what is in the product, what smoke constituents a consumer is exposed to when using the product, the impact of such exposure on the consumer, and evidence relevant to consumer perception and consumer behavior. Analysis of each of these elements is essential in order for FDA to carry out its statutory mission. In addition, because consumer behavior is responsive to promotional activity, this analysis also requires identification and analysis of packaging, ease of use, attractiveness, and other design changes, as well as the marketing materials that would accompany the introduction and promotion of the product. Thus, the regulatory requirements for submission of relevant evidence would have to include all such materials as well.

It is the responsibility of the manufacturer to provide adequate objective scientific evidence for each component of the standard. In our view, the Guidance properly lays out the minimum types of test results and criteria that are necessary. Each of the proposed studies set forth in the Guidance is essential to inform the FDA decision-making process and each is essential for FDA to be able to make the kind of health impact assessments required by the statute. For example, with respect to the risk analysis to the individual user alone, the presence of hundreds of toxic and addictive substances requires production of testing data regarding the physical properties of the product, measurements of consumer exposure when the product is used in real life situations and how changes to the product impact consumer exposure to other chemicals and smoke constituents. Although measurement of toxic substances is important, risk cannot be defined by the presence of chemical constituents of the product alone; it is more directly related to the nature and level of exposure of the tobacco user to those constituents and other chemicals that may be present in the smoke emissions of the product. Moreover, the clear statutory requirements for analysis of the likely effects of the product's availability on initiation of tobacco use by non-users and cessation by existing users require studies on whether the product increases the likelihood that non-tobacco users will start, examination of data that will allow informed judgments on the impact of the change on individuals who are in the "experimentation" stage of tobacco use as well as marketing and consumer perception studies. In considering these questions, FDA should not restrict its inquiry to data submitted by the applicant. Given the deadly nature of the product and the history of the industry's abuse of new products to increase youth tobacco use, discourage quitting and deceive consumers, the criteria established by Congress should be rigorously enforced.

General Principles for Scientific Studies

The section of the Guidance on general principles for scientific studies is particularly useful in identifying the nature of the information that studies should be designed to produce in order to address the criteria in the public health standard. The health risks associated with a

particular product should be considered in comparison to the health risks of other products, but also in comparison with whether the new product is likely to lead non-users to start, current users not to quit or current smokers to switch. New products do not exist in isolation and the relevant analysis should also seek to identify the effect introduction of such products would have on consumption of tobacco products in a market where new products are often introduced to fill a niche or appeal to a segment that might not be using tobacco products or might be contemplating quitting. Expanding consumer choice often leads to increasing the number of tobacco product users. The public health standard is also designed to require analysis of the effects of new products on the way products are actually used. The public health consequence of the introduction of a new product that displaces use of another product is very different from the public health consequence of introducing a product that is used concurrently with another product or fills a niche that makes the product appealing to a non-user. FDA's guidance explicitly asks for information that would enable the agency to distinguish between these two conditions. Product changes that deliver certain chemicals to other parts of the body or that lead consumers to inhale more deeply, or deliver chemicals differently also require the manufacturer to demonstrate with scientific evidence the impact on disease risk, addiction and usage. Provision of such information is essential for the effective implementation of FDA's authority.

FDA asks for information about the "attractiveness" of a new tobacco product to current users (especially those interested in quitting) and the "attractiveness" of the product to never-users and former-users (especially to those segments of the population that may be particularly likely to initiate or reinitiate tobacco use). We understand "attractiveness" as used in this context to mean the combination of attributes that make a product likely to increase use by a given group of users and/or potential users. Under the public health standard, FDA is required to reach decisions based on the likely impact of the introduction of a new product on initiation of tobacco use by non-users and the impact on cessation by existing users. This evidence is relevant because all tobacco products cause harm. As noted above, this standard requires the tobacco manufacturer to demonstrate to FDA that a new product will not make it more likely that non-tobacco users, especially youth, will begin, or more likely that current tobacco users will smoke more or that fewer will quit. The scientific evidence demonstrates that certain ingredients or combination of ingredients contribute to youth initiation or lead some tobacco users not to quit.²⁵ The only reason FDA does not already know more about the exact interaction of some ingredients is because the tobacco industry either hasn't done the needed testing or has done it but not disclosed it. In this case the statute is clear; the burden is on the tobacco manufacturer.

Different ingredients or tastes also impact consumer perception. For example, some cigarettes that produce a lighter feeling or smoother smoke are erroneously perceived to be

²⁵ Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), Addictiveness and Attractiveness of Tobacco Additives, 2010; Kreslake, JM, Wayne, GF, and Connolly, GN, "The menthol smoker: Tobacco industry research on consumer sensory perception of menthol cigarettes and its role on smoking behavior," *Nicotine & Tobacco Research*, Volume 10, No. 4, April 2008.

safer.²⁶ Consumer perception is also affected by packaging and marketing.²⁷ FDA must be provided data that enables it to make sound scientific assessments about consumer perception, behavior, and choice. Because these factors are elements in the analysis, the overall impact of a new product on a given segment of the public—i.e., the “attractiveness” of a product—is of central importance. “Attractiveness” is in part subject to physical measurement in terms of the smoothness or lightness of the taste and aroma, but it is in part not subject to physical measurement. The fact that not all ingredient changes are subject to physical measurements to determine “attractiveness” or “appeal” does not make the industry’s burden to provide FDA adequate scientific data any less significant. When the Congress established the public health standard and defined it according to the statutory language, it necessarily required FDA to consider and find a measure for the impact of the introduction of a product on the number of users. It is therefore not possible for FDA to fulfill its statutory responsibility without considering the attractiveness of a new tobacco product.

Materials Required to be Submitted Under the Draft Guidance

The draft guidance specifies the categories of information that must be submitted in connection with an application for marketing a new product. These categories are designed to provide FDA with the materials necessary to determine if the product meets the statutory requirements. There is strong scientific support for requiring each of the studies described in the draft guidance. Without the specified studies there will be important gaps in FDA’s knowledge. Given the harm caused by current tobacco products and the history of product change contributing to the harm, addictiveness and appeal to youth of tobacco products, it is essential that FDA not issue an order permitting a product to be marketed until the industry has provided sufficient scientific evidence on each of the issues FDA is required to consider.

Although tobacco products are regulated in accordance with the public health standard enunciated in the FSPTCA and not under the safety and efficacy standard applicable to drugs, some of the tests and measures required in order to make regulatory decisions about drugs are similar to those that are relevant in evaluating tobacco products. Of particular relevance are the tests and procedures employed by FDA in the regulation of the abuse potential of new drugs. When a drug manufacturer seeks new drug approval for a therapeutic drug that also has a potential for abuse, in addition to meeting standards for safety and efficacy, the abuse potential

²⁶ Shiffman, S., et. Al., “Smokers’ beliefs about “Light” and “Ultra Light” Cigarettes,” *Tobacco Control*; 10 (Suppl D): i17-i23, 2001; Kreslake, JM, Wayne, GF, and Connolly, GN, “The menthol smoker: Tobacco industry research on consumer sensory perception of menthol cigarettes and its role on smoking behavior,” *Nicotine & Tobacco Research*, Volume 10, No. 4, April 2008; Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), *Addictiveness and Attractiveness of Tobacco Additives*, 2010.

²⁷ Moodie, C., et. al., “Young People’s Perceptions of Cigarette Packaging and Plain Packaging: An Online Survey,” *Nicotine & Tobacco Research*, first published online October 24, 2011; Hammond, D, et al., “Cigarette pack design and perceptions of risk among UK adults and youth,” *The European Journal of Public Health* 19(6):631-7, December 2009. Hammond, D & Parkinson, C, “The impact of cigarette package design on perceptions of risk,” *Journal of Public Health* 31(3):345-53, 2009.

of the drug is also evaluated under standards established by the Controlled Substances Act. 21 U.S.C. § 811-812 Under FDA regulations, the sponsor of a drug that has a potential for abuse must submit “a description and analysis of studies or information related to abuse of the drug. . . .” 21 CFR 314.50(d)(5)(vii) In 2010 the Center for Drug Evaluation and Research (“CDER”) released Guidance for Industry on Assessment of Abuse Potential of Drugs, which discussed the kinds of information that should be included in an abuse potential submission and various approaches and methods for doing abuse potential assessments.²⁸ The guidance included discussion of preclinical screening, chemistry and manufacturing, animal behavioral pharmacology studies, application of good laboratory practice, pharmacokinetics/pharmacodynamics, human laboratory studies, clinical trial data, and postmarket experience and data. Many of the tests and procedures discussed in this guidance are relevant to the establishment of appropriate requirements for the submission of pre-market applications for new tobacco products. In the same way that toxicological tests developed for assessing the hazard potential of non-tobacco products can be applied to tobacco products, so too can tests of addictiveness that were developed to test drugs and substances be applied to tobacco products. In fact, it was the application of such tests that led the National Institute on Drug Abuse and the Surgeon General to conclude conclusively in the 1980s that tobacco was addicting. Some of these same tests have been used by the tobacco industry to better understand the addictiveness of the product and to guide product development in order to make the products more attractive.

For example, a consideration in the evaluation of a new tobacco product is the effect of the product on the body and on behavior. Thus, for example, if a variation in product constituents, such as increased sugars, results in increased acetaldehyde in smoke emissions, then these facts must be documented by established scientific methods including analytical chemistry that are used to evaluate drug product contents and the substances released from drug products and drug delivery systems when used. With respect to the effects on the body and behavior, there is broad scientific foundation and precedent that FDA and other regulatory agencies rely upon for drug evaluation that can be applied to tobacco products. The methods used to evaluate the toxicological and pharmacological effects of a product are similar whether the substances under consideration are medicinal drugs, excipients, byproducts, analytes, or inadvertent contaminants. Evaluation includes identification and quantitative characterization of the substance, and characterization of its effects on the body, including the central nervous system, and its physiological and behavioral effects.

The guidance promulgated by CDER for assessment of the abuse potential of drugs is designed to help both product developers and regulatory authorities evaluate the likelihood that a substance will be abused and cause dependence. The purpose of requiring such tests is to

²⁸ Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Draft Guidance for Industry, Assessment of Abuse Potential of Drugs January 2010, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>

prevent the initiation of use and the development of dependence as well as to understand the potential difficulty in achieving cessation from product once use has commenced. The 2010 guidance for drugs offers strategies for test selection, testing sequence, and the range of tests that have been applied to a very broad range of substances, including nicotine and other drugs used in smoking cessation medicines. Tobacco products may be more complex than drug products, but such complexity only increases the importance of following established testing procedures. The increased complexity of tobacco products may require more and different tests than those required for a new drug product in which only the dosing characteristics of a single entity have been changed as compared to a thoroughly characterized existing product.

The amount of information and the extent of testing required in connection with a new tobacco product application will vary based on the content of the new product and the degree to which it represents a departure from existing products. However, the methodology for testing new therapeutic drugs with abuse potential will in many cases also be appropriate for the testing of new tobacco products. We recommend that in the development of appropriate guidance for industry with regard to new tobacco product standards, the Center for Tobacco Products should consult with CDER to consider how the testing and information requirements established by CDER for assessing abuse potential in general should be recommended for consideration by sponsors of tobacco products to enable premarket assessment of the risk that new products may increase initiation and dependence and impede cessation.

Information Regarding the Chemical Properties of the Product

Analysis of the risks to individual smokers posed by any product depends in part on the chemical properties of the product. Section B of the proposed guidance defines the information to be submitted regarding the levels of harmful and potentially harmful constituents in the product, including smoke constituents. Pursuant to section 904, FDA has published and sought comment on a list of harmful and potentially harmful constituents. The undersigned organizations have submitted comments on this list. As indicated in FDA's notice that accompanied the list, the listing was incomplete because it included only constituents identified by other agencies as having adverse toxicological effects and did not include constituents that had not yet been systematically reviewed by relevant agencies. Moreover, the notice stated that FDA had focused only on five disease outcomes and that FDA would review other disease outcomes to assess whether the list should be augmented. In addition, the list does not include substances that impact addictiveness or addiction risk. If expanded to include these elements, the list would provide a reasonable enumeration of the constituents that should be reported in a new product application.

FDA must also take into account that neither the industry, nor the government has done testing on the full range of ingredients in cigarettes when used as part of a product that burns and is inhaled, nor have they fully tested and analyzed the impact of the different ingredients when used in the different combinations found in tobacco products. The Act makes clear that the

consuming public should no longer be treated as guinea pigs. The burden is and must be on the industry to provide data consistent with standards set by FDA prior to marketing to demonstrate that any changes are not inconsistent with their obligation to protect the public health.

It is also important that the scientific studies not only examine the chemical properties of the product, but how those chemical properties translate into the smoke inhaled by consumers or the tobacco juices absorbed by consumers of smokeless tobacco. It is not sufficient to have the manufacturer provide data on the chemical properties of the product. It is essential that the manufacturer also be required to provide test data on what the consumer receives and absorbs. It also needs to be recognized that a change in one ingredient may impact how much or in what form other ingredients in the tobacco products are absorbed or inhaled. Thus, FDA needs to require studies that go beyond focusing solely on the particular chemical or ingredient that the manufacturer has added or changed.

Studies in Adult Human Subjects

It is clear that the statutory criteria cannot be satisfied without investigations in adult human subjects and FDA appropriately includes such studies in its notice. FDA notes that such studies would involve:

Tobacco user exposure to tobacco-related compounds;

Tobacco user health risk and disease incidence;

Tobacco product use patterns (smoking topography, frequency of use, and/or use by different age groups), including evaluation of consumers' use of the new tobacco product concurrently with other products already on the market;

Abuse liability and addictiveness;

Consumer perceptions including risk perceptions based on the product itself, as well as on the packaging and labeling of the new tobacco product; and

Cessation rates for users of the new tobacco product.

Studies of adult human subjects should be required to address each of these concerns. Where biomarkers can be established biomarkers or stronger scientific evidence should be required.

Consumer perception studies are also important in determining whether the new product satisfies the public health standard. In order to ensure that the agency receives all relevant material, we recommend that FDA require production of all marketing and consumer perception studies conducted in the past by tobacco companies with regard to the development of several major new tobacco products in order to understand the types of studies the companies themselves have done in making decisions about product introduction. Review of such materials will permit FDA to formulate requirements that will enhance the likelihood that the agency receives all

relevant information. Although FDA should not limit its analysis to the kinds of studies the companies have done in the past, knowledge of the scope of such studies is an important element in ensuring that FDA receives the information it needs. Again, if a manufacturer claims an absence of adequate data, its application must be denied because it carries the burden of providing FDA sufficient data for FDA to make sound, scientific judgments.

In connection with consumer perception studies, FDA should also require production of all marketing and promotional material that would accompany the introduction of the product. Consumer perception of the product will be influenced not only by the product itself, packaging and labeling of the product but also by marketing and promotional materials. For example, promotional materials may make it evident that a proposed new product is being targeted toward underage consumers or that it is being targeted to promote the concurrent use of the product with an existing product or to promote the smoothness of the product. Consider recent advertisements for snus that are clearly designed to promote concurrent use.²⁹ Review of such materials is an important element in determining the likely impact of a new product on initiation or cessation.

Moreover, it is appropriate for the agency to require studies of risk perception even where no verbal health claim is made. Scientific literature has established that risk perceptions are often influenced by non-verbal messages.³⁰ For example, the major tobacco companies released color-coded cigarette packs to replace those with the misleading reduced harm terms prohibited by the FSPTCA and actively communicated the association to their customers, which evidence shows continues to perpetuate the long-standing, false perception of lower risk.³¹

In evaluating consumer response to the marketing of a tobacco product, it is important to understand consumer risk perception whether or not a verbal health claim is made.

FDA is also correct in requiring studies to “reflect the diversity of the US adult tobacco user population” and consider oversampling of populations particularly likely to be affected by the introduction of a particular product. With the proliferation of brands and styles and the targeting of specific products to narrow segments of the market, such analysis is particularly important.

IV. Other procedures addressed by the guidance.

Invitations to meet with the Office of Science to discuss investigational plans

²⁹ See Figure 1, US Airways magazine, October 2011 www.trinketsandtrash.org; See Figure 2, Direct Mail piece, 2010 www.trinketsandtrash.org.

³⁰ National Cancer Institute, *Risks Associated with Smoking Cigarettes with Low Machine-Yields of Tar and Nicotine; Report of the NCI Expert Committee*. National Institutes of Health. National Cancer Institute. Smoking and Tobacco Control Monograph 13, 2001

³¹ Bansal-Travers, M, et al., "What do cigarette pack colors communicate to smokers in the U.S.?" *American Journal of Preventive Medicine* 40(6):683-9, June 2011. Bansal-Travers, M, et al., "The impact of cigarette pack design, descriptors, and warning labels on risk perception in the U.S.," *American Journal of Preventive Medicine* 40(6):674-82, June 2011. Hammond, D, et al., "Cigarette pack design and perceptions of risk among UK adults and youth," *The European Journal of Public Health* 19(6):631-7, December 2009. Hammond, D & Parkinson, C, "The impact of cigarette package design on perceptions of risk," *Journal of Public Health* 31(3):345-53, 2009.

FDA's notice encourages persons who would like to study their new tobacco product to meet with the Office of Science to discuss investigational plans. We assume that the same invitation would be extended to stakeholders, such as the undersigned, who have a strong interest in understanding what the agency will require manufacturers to submit and how it will evaluate such submissions. In addition, we believe that any advice rendered at such meetings should be made publicly available on FDA's website (with appropriate protection for the confidentiality of information disclosed by potential applicants). We urge FDA to make provision for the timely disclosure of such information on its website.

Establishment of a benchmark for comparative risk to individual users

The draft guidance addresses the materials to be provided by applicants but does not indicate what baseline measure FDA will apply in evaluating the materials. In the context of measuring the risks to an individual user, it should be possible to quantify the relevant toxicants and addictive materials but a determination will have to be made as to what level of such materials is "appropriate for the protection of the public health." In the context of an application for designation of a product as "substantially equivalent" to an identified predicate product the measured amount of such materials in the predicate product constitutes the baseline. Although there are complexities because of the multiplicity of toxic materials, at least identifying the baseline for comparison is conceptually clear. There is no similar baseline for evaluating new product applications under Section 910.

The large amount of data that FDA will be receiving pursuant to section 904 should be useful in evaluating new product applications. Information drawn from such data can be used to develop a comprehensive toxicological profile, evaluate the impact of different ingredients or levels of ingredients on disease risk, or assess addictiveness or addiction risk. Even when a composite toxicological profile has been developed, however, the industry will have the burden of providing FDA with adequate scientific evidence for FDA to make a determination as to what combination of toxicants or other ingredients or constituents can qualify as "appropriate for the protection of the public health." FDA should make this determination in accordance with the broad overall purpose of the statute: the protection of the public health from a deadly group of products. Unless the manufacturer provides FDA sufficient scientific evidence for FDA that allows FDA to determine the benefit and harm of introducing the new product, the product should not be permitted on the market.

Establishment of a benchmark for risks and benefits to the public

The benchmark against which the effect of introducing the new product will be measured with regard to the risks and benefits to the public is the likely level of (1) initiation of tobacco use by current non-users in the absence of introduction of the new product; (2) cessation of tobacco use by current users in the absence of introduction of the new product and (3) harm to existing users. It is essential for the manufacturer to meet its burden of demonstrating that the

benefits of the introduction of the new product will outweigh the risks and that its introduction will not increase the number of users of tobacco products and will not decrease the number of existing users who quit.

Post-market monitoring

As noted above, the FDA's decision to permit the marketing of new products requires the agency to make assessments about the likely effect of such products on initiation and cessation. However well documented such determinations may be, FDA should be aware that such decisions could be mistaken. Products expected to have no effect on the overall public health and on initiation or cessation may turn out to have an adverse impact. As part of any determination concerning such an application, FDA should require the applicant to monitor the effects of the new product on initiation and cessation and provide periodic reports on such effects. Any order granting a new product application should be conditioned on FDA's right to evaluate the results of post-market monitoring studies and rescind the order on the basis of such studies. This is another area in which consultation with CDER, experience with postmarketing requirements and findings from drug regulation should be considered in the development of requirements for tobacco products. For example, for many addictive drugs, such as OxyContin, manufacturers must provide several lines of post-marketing surveillance to help detect initiation of use, dependence, persistence of use, and efforts to achieve cessation on a rapid and sensitive basis, (e.g., with quarterly reporting requirements.) In such cases large national surveys that provide information that is often two to three years after the real time occurrence of such effects are not considered adequate (e.g., National Survey on Drug Use and Health and the Monitoring the Future Surveys which include tobacco product measures.)

Change of policy

The requirement for this analysis as a threshold requirement for introduction of new tobacco products was designed to represent a sharp change from prior practice. Before enactment of the FSPTCA, decisions to introduce new products were made without consideration of public health concerns. Tobacco product manufacturers may object that these requirements represent a departure from existing practice. The answer to those objections is that these procedures were designed to change the governing considerations. The statute permits manufacturers to introduce new products only where they have been able to meet the statutory requirements. The statute is designed to enable manufacturers to introduce new products only where the manufacturer has affirmatively demonstrated, under the standards established in the statute, that the public health impact of such products is likely to be favorable.

Sincerely,

Campaign for Tobacco-Free Kids

American Association for Respiratory Care

American Cancer Society Cancer Action Network

American College of Preventive Medicine

American Heart Association

American Lung Association

American Psychological Association

Legacy

National Latino Tobacco Control Network

Partnership for Prevention