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Re: Docket No. FDA-2017-N-0001, Tobacco Products Scientific Advisory Committee – Written Comments re April 6, 2017 Meeting

The Campaign for Tobacco-Free Kids submits these comments in connection with the April 6, 2017 meeting of the Tobacco Products Scientific Advisory Committee on the processes used in review of tobacco products applications, including modified risk tobacco product applications (MRTP) and premarket tobacco applications (PMTA).¹

This TPSAC meeting is particularly timely for two reasons. First, within the last two years, FDA has issued its first orders denying a modified risk application for a tobacco product – the application for several Swedish snus products filed by Swedish Match – and its first orders granting an application for premarket review of a tobacco product, also for Swedish snus products marketed by Swedish Match. As discussed here, much can be learned from these proceedings going forward. Second, it is reasonable to expect that FDA will be required to expend significant resources in the near future on modified risk applications, particularly in light of the recent filing of PMI for its IQOS “heat not burn” tobacco product and the likelihood of multiple MRTP and PMTA filings for e-cigarettes, now that FDA has asserted regulatory authority over e-cigarette and other tobacco products under the deeming rule issued in May of last year.

These comments will address the scientific evaluation of both modified risk applications and premarket tobacco product applications with particular emphasis on TPSAC’s statutorily mandated role in the scientific assessment of modified risk applications.

I. MODIFIED RISK APPLICATIONS

A. Statutory Background and Role of TPSAC in Evaluating Modified Risk Applications

The Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act, or TCA) amended the Food, Drug and Cosmetic Act (FD &C Act) in part by adding §911 to regulate tobacco products marketed with modified risk claims. The TCA prohibits manufacturers from marketing tobacco products with “modified risk claims” in the absence of an FDA order authorizing such marketing. Under §911(a) and (b), a manufacturer

¹ See 82 Fed. Reg. 11226 (February 21, 2017).

must obtain from FDA a premarket order before the introduction into commerce of any product “sold or distributed for use to reduce harm or the risk of tobacco-related disease . . .” Such modified risk products include, for example, products for which the label or advertising of the product “represents . . . that the tobacco product presents a lower risk of tobacco-related disease or is less harmful” than other tobacco products.

In evaluating an application under section 911, FDA considers both the product itself and the modified risk claims sought to be made by the manufacturers. In recent cases, FDA has granted an application to market a number of new tobacco products but denied the manufacturer’s application under section 911 to make modified risk claims in connection with the products. Evaluation of a modified risk application requires analysis of both the product itself and the claims the manufacturer seeks to make in marketing it.

Under §911(g)(1), the burden is on the applicant seeking an order allowing the marketing of the product with a modified risk claim to demonstrate that the product “as it is actually used by consumers will (A) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and (B) benefit the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.”

Sec. 911(g)(4) further requires FDA to take into account the following specific empirical factors in determining whether the (g)(1) standard has been met:

- (A) The relative health risks to individuals of the tobacco product that is the subject of the application;
- (B) The increased or decreased likelihood that existing users of tobacco products who would otherwise stop using such products will switch to the tobacco product that is the subject of the application;
- (C) The increased or decreased likelihood that persons who do not use tobacco products will start using the tobacco product that is the subject of the application;
- (D) The risks and benefits to persons from the use of the tobacco product that is the subject of the application as compared to the use of products for smoking cessation approved under chapter V to treat nicotine dependence.

Thus, FDA must consider not only the effects of the asserted modified risk product on those who use it, but also its population-wide impact on tobacco use initiation, cessation and relapse, including an assessment of the likelihood that smokers would actually switch to the modified risk product. It is not enough for an applicant to show that the MRTP is less hazardous to users than other tobacco products; in order for a modified risk application to be granted, the applicant is required to show that the benefits of risk reduction to the individual (considering the likelihood of smokers switching to the modified risk product) outweigh the risks of increased initiation or diminished cessation. In short, the statute requires FDA to make scientific judgments not only about the physical effect of the product’s use, but also about the likely responses of potential consumers (both smokers and non-smokers) to the product’s marketing as a modified risk product.

Section 911 seeks to insure that any tobacco product granted MRTP status is both significantly less harmful than the tobacco products to which it is compared and that the actual population impact of its being marketed with modified risk claims will also be substantial. Products that are only marginally safer will not meet this standard. Products that may be significantly less harmful than a cigarette would not meet the standard unless the evidence is sufficient to demonstrate that cigarette smokers will actually switch from smoking cigarettes to using the product and that its marketing as a MRTP will not result in initiation by many new tobacco users and will not prompt ex-smokers to relapse. On the other hand, §911 empowers FDA to authorize

carefully crafted, scientifically based claims for products where the evidence is adequate to conclude both that the product is significantly less harmful than cigarettes or other tobacco products and that the evidence supports the conclusion that consumers will respond in a way that is likely to substantially reduce tobacco-related death and disease. The public health standard clearly gives the FDA the authority to insure that products that are likely to reduce the death toll from tobacco significantly can be promoted in ways designed to maximize the number of lives saved.

The TCA assigns TPSAC a unique and central role in FDA's assessment of whether an applicant has met its burden under §911. Unlike applications for drug approval, where the convening of an advisory committee is discretionary with FDA, the involvement of TPSAC in evaluating modified risk products is mandatory under the TCA. Sec. 911(f)(1) provides that FDA "shall refer" to TPSAC "any application" for a modified risk order. Sec. 911 (f)(2) in turn requires TPSAC to report "its recommendation on the application" to FDA within 60 days of the referral. Thus, no modified risk application can be approved or disapproved without FDA having received a recommendation from TPSAC, although the final decision on approval or disapproval rests with FDA.

Given the mandatory role of TPSAC in making recommendations on all modified risk applications, it is vital that the process for referral of such applications to TPSAC ensure that TPSAC have the opportunity for a thorough review of all the relevant scientific evidence within the 60-day referral period. The Campaign for Tobacco Free Kids presented its views at the TPSAC meeting of April 30, 2013 concerning the modified risk referral process,² submitted written comments on the issues to be addressed at that meeting and incorporates those comments by reference. Those comments emphasized: (1) the importance of FDA, prior to referral of a MRTP, having given sufficient preliminary consideration to the application to provide TPSAC substantial guidance as part of its referral; (2) the need to ensure the opportunity for public participation throughout FDA review of MRTP applications, including during TPSAC review of such applications; and (3) the importance of FDA, including TPSAC, generally following the recommendations of the Institute of Medicine in its 2012 report *Scientific Standards for Studies on Modified Risk Tobacco Products* (IOM Report).³

B. The Historical Origins of Section 911 of the TCA and Its Importance to TPSAC's Review of Modified Risk Tobacco Product Applications

In order to properly evaluate and make recommendations to FDA on MRTP applications, TPSAC must not only faithfully apply the criteria set forth in the TCA, but must also be mindful of the historical underpinnings of §911. In a very real sense, the purpose of §911 is to prevent history from repeating itself. The extensive legislative findings that Congress made in enacting section 911 make it clear Congress's intention to protect consumers from being misled by claims that some tobacco products are less harmful than others.

The provisions of §911 are based on a massive evidentiary record of fraudulent health and "reduced risk" claims made by tobacco product manufacturers over the course of more than fifty years. Those claims caused millions of Americans to initiate cigarette smoking, who otherwise would not have done so and caused millions of American smokers to continue smoking when they otherwise would have quit. In the absence of this massive industry fraud, literally millions of deaths, and untold suffering, would have been avoided.

The voluminous evidence of the industry's use of these false health-related claims was presented to the United States District Court for the District of Columbia in *United States v. Philip Morris, U.S.A., Inc.*⁴ and furnished critical support for the court's conclusion that the defendant tobacco companies had engaged in a

² Campaign for Tobacco-Free Kids, Comments filed in Docket No. FDA-2013-N-0001, Tobacco Products Scientific Advisory Committee – Referrals of Modified Risk Applications to TPSAC (April 23, 2013) (CTFK TPSAC Referral Comments).

³ The CTFK comments did take exception to IOM Recommendation #10, to the extent that Recommendation is intended to provide pre-approval to an independent third-party entity to conduct research related to a specific §911 application. See CTFK TPSAC Referral Comments at 6, n.13.

⁴ 449 F. Supp.2d 1 (D.D.C. 2006), *aff'd in relevant part*, 566 F.3d 1095 (D.C. Cir. 2009), *cert. denied*, 130 S.Ct. 3501 (2010).

conspiracy to defraud the American public so massive as to constitute racketeering under federal law. The court found:

For several decades, Defendants have marketed and promoted their low tar brands as being less harmful than conventional cigarettes. This claim is false, as these Findings of Fact demonstrate. By making these false claims, Defendants have given smokers an acceptable alternative to quitting smoking, as well as an excuse for not quitting.⁵

The court further found that the industry knew these health claims were false:

Even as they engaged in a campaign to market and promote filtered and low tar cigarettes as less harmful than conventional ones, Defendants either lacked evidence to substantiate their claims or knew them to be false. Indeed, internal industry documents reveal Defendants' awareness by the late 1960s/early 1970s that, because low tar cigarettes do not actually deliver the low levels of tar and nicotine which are advertised, they are unlikely to provide any clear health benefit to human smokers, as opposed to the FTC smoking machine, when compared to regular, full flavor cigarettes.⁶

The Surgeon General's 2012 report, *Preventing Tobacco Use Among Youth and Young Adults*, presents additional evidence that health claims by major tobacco companies, particularly those marketing light and low-tar cigarettes, may have increased youth initiation to cigarettes, citing studies showing that U.S. youth believed that "light" brands had lower health risks and lower levels of addiction than "regular" brands.⁷

C. The Importance of Congressional Findings to TPSAC's Review of Modified Risk Tobacco Product Applications

When Congress enacted the TCA and required FDA to authorize in advance any modified risk claims, it made extraordinarily detailed findings about the effect of such claims in the past. Congress found, *inter alia*:

- As the National Cancer Institute has found, many smokers mistakenly believe that "low tar" and "light" cigarettes cause fewer health problems than other cigarettes. As the National Cancer Institute has also found, mistaken beliefs about the health consequences of smoking "low tar and "light" cigarettes can reduce the motivation to quit smoking entirely and thereby lead to disease and death. TCA, §2(38)
- Recent studies have demonstrated that there has been no reduction in risk on a population-wide basis from "low tar" and "light" cigarettes, and such products may actually increase the risk of tobacco use. TCA, §2(39)
- The dangers of products sold or distributed as modified risk tobacco products that do not in fact reduce risk are so high that there is a compelling governmental interest in ensuring that statements about modified risk tobacco products are completely accurate, and relate the overall disease risk of the product. TCA, §2(40)
- Permitting manufacturers to make unsubstantiated statements concerning modified risk tobacco products, whether express or implied, even if accompanied by disclaimers, would be detrimental to the public health. TCA, §2(42)

In light of the detrimental effects of unsubstantiated or false claims of reduced risk, Congress concluded that FDA must be given authority to review modified risk products before they are put on the market:

⁵ *Id.* at 430.

⁶ *Id.* at 430-31.

⁷ U.S. Dept. of Health and Human Services, *Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General* (2012) (SG Report 2012), at 531.

- The only way to effectively protect the public health from the dangers of unsubstantiated modified risk tobacco products is to empower the Food and Drug Administration to require that products that tobacco manufacturers sold or distributed for risk reduction be reviewed in advance of marketing, and to require that the evidence relied on to support claims be fully verified. TCA, §2(43)

Thus, Congress found that “rigorous criteria” must be applied to ameliorate the risk:

- It is essential that manufacturers, prior to marketing such products, be required to demonstrate that such products will meet a series of rigorous criteria, and will benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products. TCA, §2 (36)

TPSAC’s review of MRTP applications, and its recommendations to FDA, must be faithful to the intent of Congress as reflected in these strong and specific findings.

D. Manufacturers response to enactment of Section 911.

In enacting § 911, Congress prohibited the use of specific terms in the marketing of tobacco products, such as “light, mild and low,” that had been used to lead consumers to believe that some cigarettes were less harmful than others. Manufacturers were prohibited from using such terms in the absence of FDA’s grant of an order under § 911. However, despite the fact that the TCA now expressly prohibits the use of the deceptive terms “light,” “mild” and “low-tar,” tobacco companies are using color-coding schemes to evade the ban and perpetuate the “safer cigarette” deception. Lighter-colored packaging is now used for “light” brands, and terms like “gold” and “silver” have replaced “light” and “ultra-light.” For example, consumers who previously smoked Marlboro Lights were told that they could now purchase “Marlboro Gold” and “Marlboro Silver”.⁸ Philip Morris placed notes on packs of Marlboro Lights reading “Your Marlboro Lights package is changing, but your cigarette stays the same” and directing customers to “in the future, ask for Marlboro in the gold pack.”⁹ Indeed, the company’s use of packaging colors to continue to mislead consumers was specifically noted by the U.S. Court of Appeals for the D.C. Circuit in its most recent opinion on the corrective statements ordered as a remedy for the RICO violations of major cigarette companies.¹⁰

TPSAC and FDA must ensure that the companies seeking to market MRTPs meet the standards of §911.

D. Key Tenets that Should Guide TPSAC Review of Modified Risk Tobacco Products

1. Applicant’s burden of proof

TPSAC’s consideration of MRTP applications must recognize that the burden is on the applicant to demonstrate that its product meets the §911 standards. Section 911(g)(1) permits the issuance of a MRTP order “only if the Secretary determines *that the applicant has demonstrated that such product, as it is actually used by consumers, will*” substantially reduce individual harm and benefit the health of the population as a whole (emphasis added). Although FDA is permitted to consider evidence from sources other than the manufacturer, the absence of sufficient evidence to establish any element of the §911 standard justifies a TPSAC recommendation to reject the application

2. Evaluation of harm to individual users

Even before TPSAC considers the population-wide impact of a proposed MRTP, it is required to evaluate whether the product “as it is actually used by consumers will significantly reduce harm and the risk of

⁸ Duff Wilson, “Coded to Obey Law. Lights Become Marlboro Gold,” New York Times, Feb. 18, 2010.

⁹ Duff Wilson, “FDA seeks explanation of Marlboro Marketing, New York Times, June 17, 2010.

¹⁰ *U.S. v. Philip Morris USA Inc.*, 786 F.3d 1014,1024 (D.C. Cir. 2015).

tobacco-related disease to individual tobacco users.” This, in turn, requires an evaluation of “the relative health risks to individuals of the tobacco product that is the subject of the application.” In evaluating individual risk, TPSAC should account for several key considerations.

First, because the TCA defines “modified risk tobacco product” by reference to explicit or implicit representations about the product, the evaluation of individual harm must be in reference to such representations and their likely meaning to consumers. This was, for example, a critical element in FDA’s denial of the Swedish Match modified risk application for its Swedish snus products. The application sought deletion, for the subject products, of these statutory warnings: “WARNING: This product can cause gum disease and tooth loss.” And “WARNING: This product can cause mouth cancer.” FDA determined that omission of these warning from a subset of smokeless tobacco products on the U.S. market would indicate that the products without the warning cannot cause gum disease, tooth loss and mouth cancer. Thus, FDA interpreted the application as requesting that the Swedish snus products be marketed with an implied modified risk claim that the products, as compared to other smokeless products, cannot cause gum disease, tooth loss and mouth cancer. FDA denied this application because the “totality of the scientific evidence” supports the proposition that smokeless tobacco, and the Swedish snus products in particular, can cause these conditions.¹¹

Second, TPSAC must have sufficient information concerning how the product is actually used, a requirement that is mandated specifically in §911. The way the product is consumed is important in evaluating the level of delivery of toxicants and other harmful constituents. For example, how consumers actually smoked cigarettes labeled “light,” and the consequent delivery of nicotine and toxicants to those consumers, differed greatly from the results yielded by smoking machines. Thus, it is critical for TPSAC to have available comprehensive information on conditions and manner of actual use. This should include information about the use of the product in conjunction with other tobacco products. Although a proposed MRTP may well reduce harm and the risk of disease to the individual under conditions of actual use, it is also possible for a product that appears to reduce harm under clinical conditions, or by machine measurement, to have the opposite or no effect under actual use conditions.

Moreover, a product that would benefit the individual user if used to displace the use of more hazardous products totally might not benefit such users if it is used in ways that result in the concurrent or dual use of the MRTP and other tobacco products and/or that could also discourage cessation. TPSAC’s evaluation of MRTP applications must take this consideration into account and require the production of persuasive evidence about how consumers actually use the product. It is highly relevant to determine whether consumers use the product to displace other products entirely or use them concurrently with other products. Thus, for example, in its evaluation of the Swedish Match modified risk application, FDA found that the company had not demonstrated that “U.S. consumers would use Swedish snus in the same manner as consumers in Sweden and Norway (e.g. frequency or intensity of usage; exclusive snus use versus dual use with cigarettes); therefore, we cannot conclude that, as actually used by U.S. consumers, the products would substantially reduce the risk to smokers.”¹²

Third, TPSAC should have enough evidence to evaluate whether the product increases the risk of some diseases even if it reduces the risk of others. Thus, solid scientific evidence related to multiple disease risks is required. Moreover, the assessment of multiple disease risks may be especially pertinent for certain modified risk claims. For instance, in its modified risk application for Swedish snus, Swedish Match sought to revise the currently required “WARNING: This product is not a safe alternative to cigarettes” on the label and advertising, by replacing it with this language: “WARNING: No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes.” Although FDA found evidence to indicate that the snus products, as actually used by consumers in Sweden and Norway, may substantially reduce the risks of some, but not all, tobacco-related diseases to individual users as compared to smoking cigarettes, it concluded

¹¹ FDA MRTP Application – TPL Review for Swedish Match North America, Inc. (Nov. 2, 2016), at 9-10.

¹² *Id.* at 10.

that the “scientific evidence is insufficient to support that substantial reductions would be observed across the full range of risks posed by tobacco products, as implied by a generalized statement about health risks as compared to smoking (i.e., “substantially lower risks to health than cigarettes”).¹³

Fourth, TPSAC should consider available evidence bearing on the abuse liability of the product. Although the core of TPSAC’s evaluation should be addressed to relative harm to the user when used as directed or intended by the manufacturer, TPSAC also should evaluate whether there is a risk that the product could be modified, or used in some other way, so as to increase the risk of addiction and harm.

3. Importance of pre-market testing and post-market surveillance in assessing population-wide impact

As is made clear in both FDA’s Draft Guidance on Modified Risk Tobacco Product Applications¹⁴ and in the IOM Report, assessing the population-wide impact of a MRTP requires both pre-market testing and post-market surveillance. Post-market surveillance is critical, but it should not be regarded as a substitute for pre-market consumer research to minimize the risk that the introduction of a MRTP will harm rather than benefit public health. Given the history of the tobacco industry’s fraudulent reduced risk claims and their disastrous effect on public health, it is essential that FDA and TPSAC be as fully informed as possible about MRTP products, how they will be marketed and how consumers are likely to respond to them before an order is issued allowing an MRTP claim.

4. Importance of pre-market testing assessing impact of the product, its labeling and its marketing on key audiences

Companies seeking to make a modified risk claim must be required to show not only the population-wide impact of the product, but also the impact of product labeling, packaging and marketing on consumers. Thus, FDA should require, and TPSAC should have access to, all advertising and promotional material that the applicant expects to use with respect to the product, including all testing and research the applicant has done bearing on the likely impact of such material on consumers. Because consumer behavior is influenced not only by the availability of the product, but also by the way it is labeled, packaged and marketed, TPSAC must have complete information about the intended advertising and promotional material, as well as its likely impact on consumers. FDA should be in a position to present to TPSAC the results of pre-market testing of the product and its marketing on several key audiences. In some cases applicants may apply to make modified risk claims about products that have already been on the market. In such cases, applicants should be able to provide significant information about the manner in which the product that is the subject of the application is being used and the likely consequences of its being permitted to make the modified risk claims that are the subject of the application.

First, the impact of the proposed modified risk claim and the labeling and marketing to be associated with the claim must be assessed as to tobacco users. Thus, assessing the impact of the proposed MRTP on the individual user involves consideration not only of the product, but also of how the user will react to the product and its labeling and marketing. As noted, testing must include actual use by consumers. It also should include an assessment of whether current tobacco users, when exposed to the proposed claim and the intended labeling and marketing, would use more of the product, switch to it completely from more dangerous tobacco products, or use it in conjunction with other products. Such testing must also address the extent to which users who might otherwise have quit tobacco entirely use the MRTP instead of quitting. Because quitting smoking is so difficult, smokers may look for any justification for not doing so, particularly when exposed to appealing promotional and marketing material for modified risk products. In this connection, it is important to account for the availability of FDA-approved smoking cessation products. TPSAC must address the extent to which the

¹³ *Id.*

¹⁴ Food and Drug Administration, *Modified Risk Tobacco Product Applications, Draft Guidance* (March 2012). The *Comments on Guidance for Industry on Modified Risk*, Docket FDA-2012-D-0071 (June 4, 2012) filed by the Campaign for Tobacco-Free Kids, et al. discuss in greater detail the issues addressed here and are incorporated by reference. *See also* the comments filed in Docket FDA-2013-N-0001-0056 by the Campaign for Tobacco-Free Kids, et al., which are also incorporated by reference.

availability and marketing of the proposed MRTP would diminish use of FDA-approved cessation products. If the marketing of the proposed MRTP would make smokers less likely to turn to FDA-approved products, or more likely to stop using FDA-approved products, public health may suffer.

Second, TPSAC will need to assess the impact of the proposed MRTP, and its labeling and marketing, on those who have never used tobacco. Because nearly 90% of adult smokers report that they started smoking by age 19,¹⁵ this assessment is particularly important with respect to young people. To the extent that the labeling and marketing of a MRTP influences the perception of risk by young people, it could lead them to initiate use of the MRTP when they would otherwise have remained tobacco-free. Since even adults who have never used tobacco products could be influenced to initiate with a MRTP by claims and marketing emphasizing reduced risk, this analysis of risk perception must also include adults. In addition to understanding how never-smokers might initiate with the MRTP, TPSAC also will need to ascertain whether such initiation may lead them to use other tobacco products as well. Initiation with a less harmful product may be a gateway to more harmful ones.

Third, TPSAC should evaluate the risk that the availability and marketing of a proposed MRTP may convince those who have successfully quit smoking or other tobacco use to relapse into renewed use. Even if the MRTP were minimally harmful, MRTP claims and marketing could draw former smokers back into nicotine addiction and lead them eventually to the more harmful tobacco products they were using before they quit. The health benefits of quitting smoking are well documented and may be realized relatively quickly after quitting. If the marketing of an MRTP were to lead to relapse among smokers, any benefit of the new product to current users could be offset by this impact in the broader population.

Finally, with respect to smokers, never-smokers and former smokers, TPSAC should ensure that sufficient testing and studies have been done regarding consumer understanding among populations at particularly high risk for tobacco use. This, of course, includes youth, but it also includes those with psychological conditions that render them particularly vulnerable to addiction, those in low socioeconomic status, certain ethnic minorities and the LGBT community.

5. Need for analysis of consumer perception and how consumers act based on those perceptions

In assessing the likely impact of a MRTP and its labeling and marketing on the key population groups set out above, TPSAC must evaluate the content of consumer perception of the MRTP and the likely actions consumers will take based on that perception. Deficiencies in the Swedish Match consumer perception survey were specifically cited by FDA in denying the company's modified risk application for Swedish snus.¹⁶

FDA's Draft Guidance on MRTP Applications recognizes that "FDA must ensure . . . that the advertising and labeling of the MRTP enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation to all of the tobacco-related diseases and health conditions."¹⁷ Consistent with the principle, TPSAC should have available to it sufficient studies focusing not only on the modified risk claim, but on what message consumers actually derive from the claim. For example, modified risk claims may be conveyed using numbers or percentages (i.e. presenting reductions in toxic constituents or claiming reductions in risk of certain diseases). It is important for TPSAC to determine whether consumers understand the numbers used in conveying the reduced risk, the concept of risk itself, and the implications of the claim for their personal health. If a claim is made that a MRTP reduces the risk of cancer by a quantified amount (e.g. 10%), consumer perception studies are important to determine whether consumers have an accurate understanding of what that reduction means.

¹⁵ SAMHSA, HHS, 2011 National Household Survey on Drug Use and Health (NSDUH). Calculations based on data available through Substance Abuse and Mental Health Data Archive (SAMHDA).

¹⁶ Letter from FDA to Swedish Match North America re MRTPAs (Dec. 14, 2016), at 3-4. *See generally*, Comments by Campaign for Tobacco-Free Kids and Tobacco Control Legal Consortium, Docket No. FDA-2014-N-1051, Modified Risk Tobacco Product Applications: Applications for 10 Products Submitted by Swedish Match North America, Inc. (November 14, 2014), at 33-45.

¹⁷ Draft Guidance, at 5.

FDA and TPSAC should also consider how consumers will perceive a claim that a product carries a lower risk for one tobacco-related disease, such as lung cancer, but continue to pose a risk comparable to other tobacco products for other tobacco-related diseases.

TPSAC also must be in a position to evaluate likely behavioral responses to the perceived risk. Many consumers who may understand risk do not apply it to themselves. Many smokers, particularly young smokers, overestimate their ability to quit and thus may believe the risks do not apply to them.¹⁸ TPSAC should also be cognizant of the past success of tobacco industry marketing in fostering the impression of benefits, real or imagined, from use of tobacco products and that such an impression can outweigh any risk perceptions. The marketing of an MRTP could accentuate the problem.

II. PREMARKET TOBACCO APPLICATIONS

Generally speaking, under the TCA, new tobacco products (i.e. products not on the market as of February 15, 2007), cannot be marketed without an FDA order permitting their marketing. (Products on the market as of that date are “grandfathered” and need not undergo premarket review by FDA.) Furthermore, a premarket order need not be obtained if a showing has been made that a new tobacco product is “substantially equivalent” to a grandfathered product.¹⁹ Although TPSAC does not have a statutorily mandated role in FDA consideration of premarket tobacco product applications, as it does for modified risk applications, § 910 of the TCA gives FDA discretion, either on the agency’s own initiative, or upon request by an applicant, to refer a new product application to TPSAC for its review and recommendation. Thus, it is important for TPSAC to have a thorough understanding of the underlying reasons for premarket review, the process of premarket review and the legal standards governing review.

A. Importance of Premarket Review to Public Health

The requirement of premarket review of new tobacco products has its origins in the tobacco industry’s long history of introducing new products that are more lethal, more addictive and more appealing.²⁰ Premarket review under the TCA is intended to ensure that this history does not continue to repeat itself, to the detriment of public health. The review process set out in § 910 means that the industry no longer can unilaterally decide the characteristics of the products it puts on the market. The degree to which tobacco industry product “innovation” has led to greater lethality was established by the startling conclusions of the 2014 Surgeon General’s Report, issued on the 50th Anniversary of the historic 1964 Report that established the causal link between smoking and disease. The 2014 Report concluded that, in the 50 years since the 1964 Report, the disease risk to smokers had actually increased:

Although the prevalence of smoking has declined significantly over the past one-half century, the risks for smoking-related disease and mortality have not. In fact, today’s cigarette smokers – both men and women – have a much higher risk for lung cancer and obstructive pulmonary disease (COPD) than smokers in 1964, despite smoking fewer cigarettes.²¹

The Surgeon General also found that the increase in lung cancer risk has been driven by a dramatic increase in the proportion of lung cancers that are adenocarcinoma (i.e. cancer of the lining of the lungs) and the increased risk of adenocarcinoma “results from changes in the design and composition of cigarettes since the 1950s.”²² The Report goes on to cite two such changes as the most likely causes: an increase in the levels of highly carcinogenic tobacco-specific nitrosamines (TSNAs) in U.S. cigarettes and introduction of ventilation holes in

¹⁸ Johnston, L.D., et al., *National survey results on drug use from the Monitoring the Future study, 1975-1997, Volume 1*.

¹⁹ The statute also gives FDA discretion to exempt a new tobacco product from the requirement of regulatory approval if the new product would be a minor modification of a grandfathered product. TCA §§910(a)(2)(ii), 905(j)(3)(A)(i).

²⁰ See generally, Campaign for Tobacco-Free Kids, *Designed for Addiction: How the Tobacco Industry Has Made Cigarettes More Addictive, More Attractive to Kids and Even More Deadly* (2014) (Designed for Addiction).

²¹ U.S. Department of Health and Human Services. *The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General* (2014).

²² *Id.*

cigarette filters.²³ The conclusion is inescapable that, in the more than 50 years since the landmark 1964 Surgeon General’s Report, the tobacco industry has introduced new products, and made modifications in existing products, with utter disregard for the health of their consumers.

The history of tobacco industry “innovation” also is a history of manipulating cigarettes to make them more and more addictive. According to the 2010 Surgeon General’s Report, *How Tobacco Smoke Causes Disease – The Biology and Behavioral Basis for Smoking-Attributable Disease*, cigarettes are designed for addiction. The report cites changes over the past 50 years that have made cigarettes more addicting, such as chemical additives like ammonia and sugars, tobacco blends, control of pH and control of nicotine dose. According to the Surgeon General’s factsheet summarizing the report’s findings:

The design and contents of tobacco products make them more attractive and addictive than ever before. Cigarettes today deliver nicotine more quickly from the lungs to the heart and brain. While nicotine is the key chemical compound that causes and sustains the powerful addicting effects of cigarettes, other ingredients and design features make them even more attractive and more addictive.²⁴

Finally, tobacco companies not only manipulate their products to make them more addictive, they also manipulate their products in ways that make them more attractive to starter smokers and increase the likelihood that they will become regular smokers. Thus, the number of consumers who become addicted is not just the result of design features and chemical additives that impact nicotine; it is also impacted by design features and additives that affect taste, smell and sight. For example, cigarette companies discovered that adding organic acid salts, like levulinic acid, reduces the harshness of nicotine and makes the smoke feel smoother and less irritating.²⁵

Tobacco product manufacturers have also added flavorings to reduce harshness and make new products more appealing, particularly to young people. For example TPSAC itself has determined that the addition of menthol to cigarettes masks the harshness of smoking, with the effect of increasing initiation of smoking among the young and making it more difficult to quit.²⁶ These conclusions were echoed by FDA’s own staff scientists in an extensive report issued two years later.²⁷ The impact of sweet candy and fruit flavors in making cigarettes more appealing to young people led Congress, in the TCA, to prohibit characterizing flavors in cigarettes (with the exception of menthol and tobacco flavor). Recent years have seen the emergence of small, sweet flavored cigars as well as a plethora of fruit and candy flavored e-cigarettes.²⁸ FDA’s PATH study shows that 71% of youth who smoke cigars and 85% of youth e-cigarette users, use flavored products. Moreover, 73% of youth cigar smokers and 81% of youth e-cigarette users, use the product “because they come in a flavor I like.”²⁹ There is little doubt that flavored products are attracting youth and undermining the nation’s efforts to reduce youth tobacco use.

It is critical, therefore, that TPSAC, in performing its scientific function with respect to the evaluation of new tobacco products, not lose sight of this well-documented history of the introduction of new and modified products to attract consumers and keep them addicted.,

B. Application of Statutory Standard for Premarket Review of New Products

²³ *Id.*

²⁴ U.S. Department of Health and Human Services, *A Report of the Surgeon General: How Tobacco Smoke Causes Disease – The Biology and Behavioral Basis for Smoking-Attributable Diseases* (2010).

²⁵ Designed for Addiction 23.

²⁶ TPSAC, U.S. Food and Drug Administration. *Menthol Cigarettes and Public Health: Review of the Scientific Evidence and Recommendations* (2011).

²⁷ FDA, *Preliminary Scientific Evaluation of the Possible Public Health Effects of Menthol versus Nonmenthol Cigarettes* (2013).

²⁸ See generally, Campaign for Tobacco-Free Kids, et al., *The Flavor Trap: How Tobacco Companies Are Luring Kids* (2017).

²⁹ Ambrose, BK, et al., “Flavored Tobacco Product Use Among US Youth Aged 12-17 Years, 2013-2014,” *Journal of the American Medical Association*, published online October 26, 2015.

Section 910(c)(2) of the TCA requires FDA to deny a PMTA 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.” It is clear from this language that the burden of making the required “showing” rests with the applicant company.³⁰

It also is apparent that the applicant’s burden is to demonstrate that introduction of the public is likely to reduce death and disease; that is, a new product cannot be “appropriate for the protection of the public health” unless it results in a net benefit to public health. This principle was implicitly adopted by FDA in its decision granting the PMTA to Swedish Match for its Swedish snus products, when the agency recognized that “the broad overall objective of authorizing new tobacco products to be marketed through the PMTA process is to reduce the morbidity and mortality from tobacco use.”³¹ No PMTA should be approved unless it achieves that objective.

Although the public health standard is not more specifically defined in the statute, § 910(c)(4) of the TCA makes clear the determinations FDA must make in deciding whether a product meets the standard:

- (4) Basis for finding.—For purposes of this section, the finding as to whether the marketing of a tobacco product for which an application has been submitted is appropriate for the protection of the public health shall be determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product, and taking into account –
- (A) the increased or decreased likelihood that existing users of tobacco product will stop using such products; and
 - (B) the increased or decreased likelihood that those who do not use tobacco products will start using such products.

As with modified risk products under §911, it is not sufficient for FDA to determine, for example, that the new tobacco product poses a lower risk of disease than other tobacco products on the market. Even if it poses a lower risk to the individual consumer than existing products he/she may be using, a population-wide assessment under §910 will require at least these additional questions to be answered:

- To what extent will existing users of more hazardous tobacco products switch to the new product and what will be their health gain if they do? How many of those who will switch to the new product would have ceased their tobacco use entirely if the new product had not been introduced?
- To what extent will existing users of more hazardous tobacco products engage in dual use with the new product, when they might have quit entirely in the absence of the new product? What are the consequences of such dual use on the individual user’s health?
- To what extent will use of the new product be a step toward complete cessation of tobacco products by the user?
- To what extent will those who have never used tobacco products initiate use with the new product and what will be the individual health consequences of initiation?
- To what extent will those who once used tobacco products re-initiate use with the new product and what will be the individual health consequences of such re-initiation?
- To what extent will initiation or re-initiation lead users to use more hazardous tobacco products when they would not have used such products in the absence of the new product?

³⁰ Section 910(c)(2) also requires denial of the PMTA if there is a failure to confirm to good manufacturing practices, the proposed labeling is false or misleading or the product fails to conform to a product standard in effect.

³¹ Food and Drug Administration, Center for Tobacco Products, Office of Science, *Premarket Tobacco Application (PMTA) Technical Project Lead (TPL Review Swedish Match North America, Inc.)* (November 3, 2015)(Swedish Snus TPL Review), at 34.

Thus, it is apparent that TPSAC’s scientific expertise may be required, not only on the physical aspects of the product and its physical impact on the user, but also on a host of behavioral issues requiring an informed assessment of how the product will be used and how its use will affect the use of other tobacco products. Moreover, the full range of these issues will require an analysis of the product’s intended packaging and marketing, in addition to its physical characteristics.

C. FDA’s Application of the Statutory Standard to Swedish Snus Products

The interaction between the scientific assessment of individual harm and a similar assessment of population-wide impact is instructively shown by FDA’s consideration of the Swedish Match PMTA for its Swedish snus products. Several of FDA’s conclusions are particularly notable.

First, the agency concluded that, because the Swedish snus products contain significantly lower levels of NNN and NNK, two of the most carcinogenic constituents in tobacco products, than over 97% of the smokeless tobacco products on the U.S. market, if current smokeless users switched to Swedish snus, their excess cancer risk would be lowered significantly. FDA estimated that the reduction in excess risk would be 90% compared to use of moist snuff (market share: 82%), 67% compared to use of chewing tobacco (market share: 15%), 38% compared to use of US-style snus, and 92% compared to use of dry snuff.³² Thus, FDA concluded that, when used exclusively instead of other U.S. market smokeless tobacco products, Swedish snus products offer a “potential for reductions in oral cancer.”³³ However, FDA made no assessment of the likelihood that current users of other, more hazardous, smokeless products would switch to Swedish snus.

Second, FDA found that, when used exclusively instead of cigarettes, Swedish snus products offer lower risk of developing respiratory diseases (i.e. COPD, emphysema, chronic bronchitis) and certain cancers (such as oral, esophageal and lung).³⁴ However, FDA also found, based on clinical trials and the experience with similar Swedish snus products on the U.S. market, that “it is unlikely that a significant portion of US cigarette smokers will switch exclusively to these Swedish snus products”³⁵

Third, FDA found that uptake of Swedish snus by nonusers is likely to be “very low,” relying on the actual market experience of “very similar” Swedish snus products that currently exist, for which “no increase in product use has been reported.”³⁶ Thus, FDA’s analysis of the potential for nonuser uptake was strongly informed by the experience with similar products already on the market. FDA found that “[s]nus products are a small minority of tobacco products sold in the US and epidemiological data indicate that use rates remain relatively low. . . .”³⁷

It is apparent that FDA’s decision to grant the Swedish Match application was based on two central findings: (1) that the individual health risks from Swedish snus are significantly lower than the risk of other smokeless tobacco products on the U.S. market or cigarettes; and (2) that because snus products generally have not proven to be popular in the U.S., there is little likelihood that the availability of Swedish snus will lead to greater initiation. As FDA summarized its findings:

Current low snus adoption rates suggest that, any detrimental effects to the US population from market these products are likely to be minimal. Overall, it is anticipated that unless use patterns change in unfavorable ways (increased youth initiation, delayed/decreased cessation), the products which are the subject of these applications may decrease the individual risk among

³² Swedish Snus PTL Review, at 37.

³³ *Id.*

³⁴ *Id.*

³⁵ *Id.* at 36.

³⁶ *Id.*

³⁷ *Id.*

current ST [smokeless tobacco] users due to their favorable toxicological profile without posing increased risk to the general population.³⁸

Thus, the agency approved the Swedish Match PMTA “so that current ST users who chose to continue using tobacco products will have additional options for less toxic smokeless tobacco products, thereby potentially decreasing the negative health impact from tobacco product use.”³⁹ Given current use patterns suggesting a low risk of increased initiation or decreased cessation of tobacco products, FDA approved the application based on Swedish snus as affording an “additional option” for less toxic smokeless tobacco, though FDA cited no evidence suggesting that U.S. smokeless users are likely to switch to Swedish snus.

The agency’s analysis of the Swedish Match PMTA demonstrates the complex interaction between the assessment of individual risk and population-wide effects of new tobacco products under review. Certainly, if current use patterns of similar Swedish snus products had supported a greater risk of tobacco product initiation (particularly among young people) or decreased cessation, FDA may well have concluded that it could not grant the application absent more evidence that smokeless users and cigarette smokers would actually switch to the lower risk Swedish snus. Other products that are the subject of PMTAs in the future may well pose a greater risk of initiation, or decreased cessation, than that found to be the case for Swedish snus. Such a heightened risk of adverse population-wide effects presumably would require substantial evidence that significant numbers of current users of higher-risk products, who would not otherwise have quit, would switch to the lower-risk product, in order for the public health standard to be met.

III. CONCLUSION

The Tobacco Control Act contemplates the involvement of TPSAC (required for MRTPs and discretionary with FDA for PMTAs) in assisting FDA in its scientific evaluation of both modified risk products and new tobacco products. In discussing with TPSAC the processes used in FDA review of tobacco product applications of both kinds, FDA should emphasize two overarching themes.

First, TPSAC must understand that the statutory provisions requiring FDA review of modified risk products and new tobacco products are responses to the tragic history of tobacco industry conduct in using false claims of reduced risk and the introduction of new products to keep consumers smoking and to attract new smokers. It is the responsibility of FDA and TPSAC to ensure that these statutory provisions are implemented to protect the public from this kind of industry conduct that would threaten the nation’s considerable progress in curbing smoking, particularly among young people.

Second, TPSAC must understand that, with respect to both modified risk products and new tobacco products, rigorous science will need to be applied, both in assessing the risk of products to individual tobacco product consumers and in analyzing the impact of products on the population as a whole. The complex interaction between individual risk and population-wide impact is perhaps the most challenging component of FDA’s role as to both modified risk and new tobacco products. TPSAC has the potential to offer invaluable assistance to the agency in meeting that challenge in the interest of public health.

Respectfully submitted,

Campaign for Tobacco-Free Kids

³⁸ *Id.*

³⁹ *Id.* at 37.