



December 16, 2019

Dockets Management Staff
 5630 Fishers Lane, Room 1061
 Rockville, MD 20852

Re: Docket No. 2019-N-2854

Ladies and Gentlemen:

The undersigned organizations hereby submit this comment in the above-designated docket on the proposed rule for Premarket Tobacco Product Applications and Recordkeeping Requirements. The proposed rule is designed to inform tobacco product manufacturers and the public about requirements for submission of Premarket Tobacco Product Applications (“PMTAs”), related recordkeeping requirements, requirements for post-market information gathering and reporting, and the process FDA will use in the evaluation of PMTAs. These comments will address each of these areas in turn with principal emphasis on the requirements for submission of PMTAs. These comments are largely directed toward the requirements for submission of PMTAs for ENDS products, which are likely to be the subject of most PMTAs submitted in 2020, but include discussion related to other tobacco products where pertinent.

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SUMMARY OF MAJOR POINTS

1. FDA should recognize that for the vast majority of products likely to be the subject of applications submitted in 2020, it will be conducting post-market rather than pre-market review because many of these products have been on the market for years without prior authorization.
2. Because most of the products that will be subject of PMTA applications submitted in 2020 will be for products that have been marketed and promoted for several years, FDA should require production of comprehensive information on advertising, promotion, marketing, pricing, sales, user demographics, addiction and abuse potential and health harms of such products from the first introduction of the product into commerce to the date of the application.
3. FDA should require direct evidence regarding the risk perception of the product by U.S. youth and usage by U.S. youth in the evaluation of PMTAs and should not rely solely on surveys of young adults or foreign data in assessing the impact of a new tobacco product on youth. Where a specific product has not been on the market, such data should be presented for other products with similar characteristics.
4. FDA should not grant PMTAs for ENDS products where the product design allows consumers to alter abuse liability and health risks by manipulating factors that impact nicotine delivery because such product design does not permit accurate assessment of abuse liability or health risk.
5. FDA should take into account the impact of the use of nicotine salts on abuse liability and should prohibit the use of nicotine salts unless the product, as actually used, meets an established, scientifically appropriate ceiling for nicotine delivery.
6. FDA should not grant a PMTA for a product if another product in the same category is as effective at helping users of combusted products switch completely and is less likely to cause nonusers of tobacco products to initiate tobacco use.
7. The Tobacco Control Act makes clear that showing that a new tobacco product is less toxic or less harmful than a cigarette is an insufficient basis for the issuance of marketing order.
8. Because any health benefit to current cigarette smokers requires a smoker to stop cigarette smoking completely, FDA should require scientific evidence to demonstrate that an individual ENDS product enables smokers to switch completely.
9. FDA should not grant a PMTA for a flavored product without scientific evidence to demonstrate that the flavor is necessary for adults to switch completely from smoking, will not attract youth users, and does not increase the toxicity of the product.

10. FDA should require clear rules governing how and to whom a product is marketed to limit its marketing to adult smokers to enable them to stop using combusted tobacco products completely and to prevent marketing that will attract youth.
11. FDA should adhere to the statutory criteria in evaluating a PMTA, including the requirement for submission of sufficient scientific evidence to demonstrate that the issuance of a marketing order is appropriate for the protection of the public health (“APPH”).
12. FDA should require evidence of the impact of the product on population groups especially vulnerable to tobacco use and industry exploitation to ensure that introduction of products will diminish health disparities.
13. The identity of products for which PMTAs are sought should be publicly disclosed and stakeholders other than the applicant should be permitted to provide information for consideration in the evaluation of PMTAs. The proposed rule, which states that the identity of applicants and products for which PMTAs are sought will be kept confidential, is contrary to the Freedom of Information Act and inconsistent with current FDA practice.
14. PMTAs raising significant policy issues should be referred to the Tobacco Products Scientific Advisory Committee (“TPSAC”).

I. REQUIREMENTS FOR THE SUBMISSION OF PMTAS

The purpose of a PMTA is to provide FDA with all the information necessary to determine whether to grant or deny an order permitting a manufacturer to market a new tobacco product pursuant to Section 910(c) of the Tobacco Control Act, 21 USC 387j(c), which identifies the findings and determinations FDA must make in reaching its decision. Section 910(c)(2) directs FDA to deny an application if (1) 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” (“APPH”); (2) the methods used in, or the facilities used for, the manufacture processing or packing of such tobacco products do not conform to [Section 906(e) of the Act, 21 USC 387f(e)]; (3) based on a fair evaluation of all material facts, the proposed labeling is false or misleading in any particular; or (4) such tobacco product is not shown to conform to a tobacco product standard.

The statute further elaborates on the requirements for showing that the marketing of a new tobacco product is APPH. Section 910(c)(4) directs FDA to determine whether the marketing of a new product is APPH based on “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 products 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.” This provision makes it clear that a showing that an e-cigarette is less toxic or carcinogenic than a cigarette would be insufficient to establish that the grant of an application would be APPH; rather, a finding that the marketing of a new tobacco product is APPH would have to be based on the impact of the new product on both existing users of tobacco products and nonusers, including youth.

The statute also identifies several categories of information that an application must contain:

(A) full reports of all information, published or known to, or which reasonably be known to, the applicant, concerning investigations which have been made to show the health risks of such tobacco product and whether such tobacco product presents less risk than other tobacco products;

(B) a full statement of the components, ingredients, additives, and properties, and of the principle or principles of operation, of such tobacco product;

(C) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and, when relevant, packing and installation of, such tobacco product;

(D) compliance with applicable product standards;

(E) samples of the tobacco product and components thereof;

(F) specimens of labeling proposed to be used; and

(G) such other information as FDA may require.

The statute requires that the manufacturer of a new tobacco product bear the burden of establishing each element of the statutory requirement. As stated by the United States Court of Appeals for the District of Columbia in its recent decision upholding the validity of the premarket review provisions of the Deeming Rule,¹

The premarket approval requirement is in the Act. It was Congress, not the FDA, that imposed it on new tobacco products, including e-cigarettes. There is no exemption in the Act for certain new tobacco products speculated to be less risky than other new tobacco products. Only tobacco products consistent with the population-effects standard fulfill the Act’s requirement that each new tobacco product’s risks not outweigh its benefits to the public health. Once the FDA deemed e-cigarettes to be ‘tobacco products’, . . . e-cigarettes became subject to premarket authorization and the requirement to meet the population-effects standard. The ‘FDA is not authorized to deviate from this statutory standard.’

¹ *Nicopure Labs, LLC v. FDA*, Case No. 17-5196, Document No. 1819471 at 25 (D.C. Cir. Dec. 10, 2019).

In evaluating the proposed rule, the undersigned organizations focus on whether the proposed rule (1) provides FDA with all the information needed to determine whether granting the application would be APPH; and (2) requires provision of all the information specified in the statute. The most important areas of inquiry for FDA in the evaluation of PMTA applications are (1) investigations of the health risk of the product and (2) information about the risks and benefits to the population as a whole.

II. FOR PRODUCTS ON THE MARKET AS OF THE DATE OF THE PMTA, THE PROPOSED RULE SHOULD BE AMENDED TO REQUIRE MANUFACTURERS, AS PART OF THE APPLICATION, TO SUBMIT THE SAME CATEGORIES OF INFORMATION REQUIRED FOR POST-MARKET REPORTS.

The proposed rule properly interprets the goal of section 910(b)(1)(A) as ensuring that FDA has “a complete understanding of the existing information about a new tobacco product.” Unfortunately, the proposed rule fails to provide FDA with the information necessary to have a such an understanding. The most significant shortcoming of the proposed rule stems from FDA’s failure to take account of the fact that a large number of the products that will be the subject of early PMTAs have actually been on the market for years and that considerable evidence regarding the consequences of their marketing and their use is available and highly pertinent to the APPH determination. Although the PMTA provisions of the statute refer to “premarket” review, in fact the review FDA will be conducting for applications filed in 2020 will be “post-market review” for many, if not most products. Rather than recognizing this fundamental fact and requiring the submission of evidence based on what has actually happened, the rule fails to require applicants to provide information that it is the responsibility of the manufacturer to collect about products that they have been marketing for years. FDA cannot discharge its statutory responsibility to protect the public health if it fails to require provision of this information.

It is not difficult to identify this information: it is essentially the same information that FDA is proposing to require companies to provide in post-market reports in section 1114.41. FDA has properly deemed this information relevant and required it to be provided for periods subsequent to the grant of a PMTA. In fact, however, because the vast majority of products that will be the subject of PMTAs in 2020 will have been on the market for years, for these products the PMTA process is in actual fact already a post-market review. The same information regarding the marketing and use of the product that is relevant for what FDA deems post-market review in section 1114.41 is relevant in determining whether a PMTA should be granted. Moreover, given the fact that FDA’s consideration of applications will be taking place at a time when youth usage of ENDS products is at epidemic proportions, the failure to take proper account of the conduct and market conditions that produced this epidemic would prevent FDA from properly addressing a major public health crisis.

A. The proposed rule should be amended to require provision of comprehensive information about the way a product has been advertised, promoted, marketed, and priced from its introduction to the market until the date of the application.

FDA itself acknowledges that information regarding advertising, marketing and promotion of tobacco products is important in determining whether the marketing of a product is APPH. FDA correctly notes that there is a well-established body of scientific evidence demonstrating the effect of advertising and marketing on youth and young adult tobacco use. 84 Fed. Reg. at 50581. As FDA points out, “marketing plans can provide important information regarding whether permitting the marketing of the new product would be APPH” and would “help [FDA] understand and prevent or minimize the potential harm that could be caused by the marketing of a new tobacco product.” 84 Fed. Reg. at 50580. Because of the close relationship between marketing and youth usage, FDA is correct in observing that the applicant’s marketing plans “will help FDA determine ... the likelihood of changes in tobacco product use behavior ... and evaluate potential youth access to and youth exposure to labeling, advertising marketing, or promotion of, new products.” 84 Fed. Reg. at 50581. FDA notes that heavy use of online social media “indicates the potential for” youth exposure. *Id.*

Moreover, the proposed rule repeatedly acknowledges the importance of advertising, promotion and marketing in influencing consumer risk perception—especially among youth—and in stimulating consumption of tobacco products, including ENDS products, by adolescents. FDA correctly notes that perceptions of the risk of the product may influence decisions to use the product and the resultant exposure to health risks and it concedes that advertising, marketing, promotion and labeling are key elements in shaping those perceptions. 84 Fed. Reg. at 50606-50607. Moreover, in recognition of the importance of advertising, promotion and marketing in influencing risk perception and product usage, the proposed rule seeks an appropriately detailed list of items regarding advertising, promotion and marketing for post-market review. Sec. 1114.41(a)(1)(vii-x). In addition, the proposed rule states that if a PMTA does not contain substantive information regarding the potential impact of the product and its label, labeling and advertising on individuals’ perception of the product and their use intentions, FDA intends to refuse to file the application. 84 Fed. Reg. at 50606. The proposed rule also states that because advertising, marketing and promotion of a tobacco product can have a significant impact on the potential for tobacco product initiation, especially by youth, where FDA is unable to determine the impact of labeling, advertising, marketing and promotion on consumer perceptions and use intentions, FDA intends to issue a no marketing order. *Id.*

Despite making these numerous acknowledgments of the importance of advertising, marketing and promotion in shaping consumer risk perception and influencing usage of ENDS products, particularly among youth, FDA has failed to require sufficient information about advertising, marketing and promotion, including price promotions, to enable it to determine whether the marketing of a product is APPH. Many of the products that will be the subject of PMTAs have been commercially marketed for years. Marketing plans for the future build on the

image of the product created during the entire period in which it has been commercially marketed and they cannot appropriately be evaluated without reference to the marketing history of the product. In order to evaluate the potential effect of any marketing plan for future years, FDA must require *all* the information listed in Proposed Rule §1114.7(f)(2) and that information must be required for the entire period during which the product has been commercially marketed, including intended target audiences, media and distribution channels, specific tactics, total dollar amounts of media buys and marketing and promotion activities, and timing for the activities. Although in the section of the rule on post-market review FDA has identified the types of information on marketing activities that must be provided, it has not required this information for a sufficient period of time. *FDA cannot properly evaluate marketing information unless it has complete marketing information for the entire period during which the product has been commercially marketed.*

The current epidemic of youth usage of e-cigarettes, largely fueled by Juul and Juul imitators, underscores the crucial role youth-oriented advertising, marketing and promotion have played in causing a public health catastrophe. Materials produced in hearings before the Subcommittee on Economic and Consumer Policy of the Committee on Oversight and Reform of the U.S. House of Representatives have documented the extensive marketing campaign conducted by Juul beginning even before Juul's first products were commercially marketed and demonstrated the connections between this marketing and the youth e-cigarette epidemic.² Juul's marketing campaign directed at youth was detailed in a recent *New York Times* article and in a complaint recently filed by the State of California.³ This sophisticated marketing campaign was modeled on the marketing campaigns conducted by the major tobacco companies over the course of many decades that led to the epidemic of youth usage of combusted cigarettes that was exhaustively documented in the decision of the United States District Court for the District of Columbia in *U.S. v. Philip Morris*, 449 F. Supp. 2d 1 (D.D.C. 2006), *aff'd in relevant part*, 566 F. 3d 1095 (D.C. Cir. 2009). The fact that Altria now owns a major stake in Juul and that the top executives of Juul are former Altria executives further demonstrates the need for FDA to acquire a complete understanding of the marketing campaigns that have led to the dominant market position Juul products have come to enjoy.

² House Committee on Oversight and Reform, "New Documents Show JUUL Deliberately Targeted Children to Become the Nation's Largest Seller of E-Cigarettes," Press Release, July 25, 2019, <https://oversight.house.gov/news/press-releases/new-documents-show-juul-deliberately-targeted-children-to-become-the-nation-s>. House Committee on Oversight and Reform, "Examining JUUL's Role in the Youth Nicotine Epidemic: Part I," Hearing, July 24, 2019, <https://oversight.house.gov/legislation/hearings/examining-juul-s-role-in-the-youth-nicotine-epidemic-part-i>. House Committee on Oversight and Reform, "Examining JUUL's Role in the Youth Nicotine Epidemic: Part II," Hearing, July 25, 2019, <https://oversight.house.gov/legislation/hearings/examining-juul-s-role-in-the-youth-nicotine-epidemic-part-ii>.

³ Creswell, J & Kaplan, S, "How Juul Hooked a Generation on Nicotine," *New York Times*, November 24, 2019; *People of the State of California v. Juul Labs, Inc.*, Superior Court, County of Alameda, Case No. RG 19043534, filed November 18, 2019.

Accordingly, FDA should amend the proposed rule to seek all the information specified in Section 1114.41 regarding advertising, marketing and promotion but require provision of this information for the entire period from the first advertisements for the product until the date of the application. This information includes all of the following items specified in Section 1114.41.

These include of the following, all of which are required for post-market reporting:

- Full color copies of all advertising for the product from the date it was first advertised to the date of the application;
- A description of the implementation of all advertising and marketing plans, by channel and by product, and the dollar amounts and flighting of such plans, by channel, including
 - (A) use of competent and reliable data sources, methodologies, and technologies to establish, maintain and monitor highly targeted advertising marketing plans and media buys;
 - (B) Targeting of specific adult audiences by age-range(s), including young adults, ages 18 to 24, and other demographic or psychographic characteristics that reflect the intended target audience, including a list of all data sources used to target advertising and marketing plans and media buys;
 - (C) Actions taken to restrict youth-access and limit youth-exposure to the product's labeling, advertising, marketing and promotion;
 - (D) Use of owned, earned, shared, or paid social media to create labeling for, advertise, market or promote the products;
 - (E) Use of partners, influencers, bloggers, or brand ambassadors to create labeling for, advertise, market, or promote the product;
 - (F) Consumer engagements conducted by the applicant, on its behalf, or at its direction, including events at which the products were demonstrated;
 - (G) Use of earned media or public-relations outreach to create labeling for, advertise, market, or promote the products;
 - (H) An analysis of the actual delivery of advertising impressions, by channel, by product and by audience demographics, including a breakout by age-group, verified against post-launch delivery-verification reports submitted to the applicant from an accredited source.

In addition, FDA should require an analysis of the effect of the marketing programs detailed above on the perceptions and attitudes of the audiences reached by these materials. In

cases where advertising, promotion and marketing materials refer to a group of products or a product line, FDA should require production of all the same materials and require an application for any individual product within such a group or product line to incorporate all such materials by reference. Where an application is filed for a product that has not been marketed before, FDA should require production of all such information for all similar predecessor products.

FDA cannot properly evaluate a PMTA application without provision of all this information.

B. The proposed rule should be amended to require provision of all information about the sales and distribution of the product from the time it was introduced to the date of the application.

FDA cannot properly evaluate a PMTA application without information on the sales and distribution of the product from the time it was introduced to the date of the application. That a product has a substantial share of the market and may have generated hundreds of millions of dollars in sales revenue is relevant in evaluating the population level consequences of granting a marketing order.

The information that FDA has requested in post-market review regarding sales and distribution should be required to be submitted as part of the PMTA for the entire period from the first sales of the product up until the date of the application. FDA should require full information about the sales of the product reported in dollars, units, and volume with breakdowns by U.S. census region, major retail markets, and channels in which the product is sold *for the entire period from the date the product was first commercially marketed to the date of the application.* (cf., Sec. 1114.41(a)(vi)(A)). The sales information required should include sales through all outlets, including non-sanctioned sales such as those through eBay, Craigslist and other platforms. For the same reason this information is relevant for post-market reporting, it is equally relevant in the consideration of the PMTA. As written, the proposed rule does not even require this information as of the date of the application. Where an application concerns a product that has not been marketed before, the applicant should be required to provide such information for all similar predecessor products.

C. The rule should be amended to require information about the demographic characteristics of product purchasers and users, such as age, gender and tobacco use status for the entire period from the date the product was first commercially marketed and the date of the application. (cf., Sec. 1141(a)(vi)(C))

Given the epidemic of youth usage of e-cigarette products, information about the demographics of usage of the product during the entire period for which it has been on the market is among the most important types of information that FDA could require. It is essential for FDA to have information not only about total usage of the product but also about the age, gender and tobacco use status of the consumers using it. FDA cannot adequately discharge its obligation to evaluate the risks and benefits to the population as a whole if it does not require this

information about the consumers who are using the product. Moreover, in light of the large influence of flavors on youth usage of tobacco products, including ENDS products, this information should be required for each flavor. Manufacturers who have been selling a product for years should be expected to have information about the demographic characteristics of the consumers who have been using their products and they should be required to provide it.

D. FDA should require applicants to provide all information on the topography of usage by each demographic class of users for the entire period during which the product has been sold.

As FDA acknowledges, the health effects of a product depend in substantial part on the topography of product use, including frequency of use, use in combination with other tobacco products, ability of a consumer to change product design and add or subtract ingredients, ability of a consumer to vary temperature, voltage and wattage, etc. Data on the way consumers actually use the product is thus essential to any evaluation of the product's effect on health.

E. The information regarding product changes that is required to be provided in post-market reports (Sec. 1114.41(1)(ii) (A)-(B)) should be required for all changes in the product from the date it was first introduced into commerce until the date of the application.

Many of the products for which PMTAs will be filed in 2020 have undergone changes since the date they were first introduced. In requiring information regarding use of the product for the entire period of its marketing FDA should require comprehensive information on all of changes in the product since the date it was first introduced into commerce until the date of the application.

III. INFORMATION ABOUT THE HEALTH RISKS OF THE PRODUCT AND WHETHER IT PRESENTS LESS RISK THAN OTHER TOBACCO PRODUCTS

The proposed rule properly interprets the goal of section 910(b)(1)(A) as ensuring that FDA has “a complete understanding of the existing information about a new tobacco product.” The statute requires provision of information about two different aspects of the health risks: (1) the health risks of the product and (2) whether such tobacco product presents less risk than other tobacco products.

The proposed rule properly identifies the major categories of health risks presented by tobacco products and the types of information that should be provided regarding these categories. Sec. 1114.7(k), 84 Fed. Reg. 50650-51. In evaluating the sufficiency of the health risk investigations submitted by an applicant, FDA should take into account the fact that many products for which it will receive applications will have been on the market for more than three years. Manufacturers with products currently on the market should have investigated the health risks created by the widespread actual use of their products over a substantial period of time.

Given the opportunities for investigation presented by the actual use of these products, those manufacturers should reasonably be expected to have thoroughly investigated the health risks posed by their products and resorting to alternatives such as “bridging studies” should be the exception and not the rule. FDA properly proposes to require that the use of bridging studies be accompanied by “a scientific rationale to justify why the study findings apply to its new tobacco product” but the rule should also require an explanation of why a direct investigation of the new product itself was not provided. (See section III.K, *infra*).

The proposed rule properly takes a broad view of what constitutes “investigations regarding the potential health effects of their product.” Sec. 1114.7(k)(1)(i)(A). For these purposes, investigations of the health risks of a product include “full reports of investigations on the constituents, including HPHCs, in the specific product or formed during use of the product.”

A. Toxicological Profile

FDA properly requires production of all investigations regarding the toxicological profile of the product and lists a wide variety of health effects known to be caused by tobacco products. It also properly recommends that an applicant compare the toxicity of its product to that of other products in the same category. For example, as with all other aspects of health risk, the toxicity of various ENDS products in comparison with each other is relevant in determining whether FDA grants a PMTA. (See section III.D, *infra*.) FDA’s evaluation of whether an application should be granted may depend not only on whether a product is less toxic than combusted products, but also how its toxicity profile compares with those of other tobacco products that may be no less effective in providing an alternative to combusted products.

B. Pharmacological Profile

FDA also properly requires production of all investigations concerning the pharmacological profile of the product. Sec. 1114.7(k)(1)(i)(C). All the same considerations applicable to toxicity studies and the relative toxicity of various products in the same category apply to the pharmacological profile of various products. As FDA notes, the pharmacological profile of a tobacco product “provides important information regarding how the product constituents and human body interact with each other.” For example, as FDA notes, the abuse potential of nicotine increases when absorption is rapid because the rewarding properties of the compound increase, and suppression of withdrawal symptoms occurs more quickly.”

C. Patterns of Use

Importantly, the proposed rule requires full reports of all investigations regarding the health risks of the product compared to using other tobacco products, never using tobacco products, quitting tobacco use, and using the product in conjunction with other products. Sec. 1114.7(k)(1)(i)(D). FDA properly proposes that applicants include comparisons between the health risks of the product and never using a tobacco product. 84 Fed. Reg. at 50605-50606. As

FDA notes, this information is relevant to determining the health risks faced by nonusers who initiate tobacco use with the tobacco product. FDA also properly requires the inclusion of comparisons between the health risks of the tobacco product and dual or poly-use of tobacco products because, as FDA notes, such dual or poly-users may continue to face the potentially higher health risks of the more dangerous product. 84 Fed. Reg. at 50605. In addition, FDA properly requires applicants to submit information to help the agency determine the health risks to former smokers who begin using the products. 84 Fed. Reg. at 50606.

D. Whether Such Tobacco Product Presents Less Risk Than Other Tobacco Products

The statute also requires the health risk inquiry to include consideration of “whether such tobacco product presents less risk than other tobacco products.” The proposed rule makes it clear that consideration of comparative risk for an ENDS product includes not only a comparison to other classes of tobacco products, such as combusted products, but also a comparison to other ENDS products. Although even if some percentage of ENDS products present lower risk than combusted tobacco products, there may be a wide variation in health risk among various ENDS products and the proposed rule properly requires the manufacturer to provide health risk information in comparison to other ENDS products. For example, consider two hypothetical ENDS products, Product A and Product B, both of which present substantially lower risk than cigarettes. If one assumes that Product A nevertheless presents a substantially lower health risk than Product B and is just as likely to displace the usage of cigarettes, FDA might well conclude that it should grant the PMTA for Product A and deny it for Product B. The fact that one product may present a lower health risk than cigarettes does not support the conclusion that all PMTAs for products in that category should be granted.

Moreover, the proposed rule properly states that FDA will review the health risks associated with changes in tobacco product use behavior in all the various aspects of such behavior, including initiation, switching, poly-use, dual use, cessation, and relapse that may occur with the marketing of the new product. The proposed rule encourages applicants to compare their products with other products in its category with regard to each of these outcomes and concludes that “this comparative health risk data is an important part of the evaluation of the health effects of product switching.” 84 Fed. Reg. at 50600. FDA properly advises applicants to compare their products to those products that consumers are most likely to consider interchangeable. *Id.* For instance, data show that U.S. smokers are less likely to switch from cigarettes to smokeless tobacco,⁴ and therefore a new smokeless tobacco product might most appropriately be compared to another smokeless tobacco product.

⁴ A 2009 study based on data from the California Tobacco Survey showed that the majority of daily smokers were not interested in switching their cigarettes for smokeless tobacco. In fact, 87 percent of smokers said they were “definitely not” or “probably not” open to the idea of replacing their cigarettes with smokeless tobacco, compared to only 12.7 percent of the smokers who reported that they “definitely” or “probably” would consider it. [Timberlake, D, “Are smokers receptive to using smokeless tobacco as a substitute?” *Preventive Medicine* 49(2-3):229-32, 2009, <http://www.ncbi.nlm.nih.gov/pubmed/19631684>.] A national cross-sectional study of current and former smokers

E. Effects of Label, Labeling and Advertising on Tobacco Use Behavior

Very importantly, FDA correctly interprets health risk investigations to include “the effect of the product and its label, labeling, and advertising on tobacco use behavior and tobacco use topography because behavior and topography are directly related to levels of exposure to HPHCs, which, in turn, impacts health risks.” 84 Fed. Reg. at 50604. FDA notes that aspects of a product that could result in more frequent or intense use compared to currently marketed products can include differences in the appeal and design of the product, including ingredients, flavors, alteration in nicotine delivery, changes in velocity of inhaled particles, effort required to inhale, or the density of the aerosol. *Id.* Despite this recognition, as noted above, the proposed rule does not require production of adequate information for FDA to evaluate the effects of labeling, advertising, marketing and promotion on the risks and benefits of granting a PMTA. For those products currently on the market that are the subject of PMTAs, FDA should require – for the entire period from the time the product was first advertised until submission of the application – comprehensive production of all the categories of advertising, marketing and promotional materials that are currently listed in the proposed rule for post-market review (Sec. 1114.41).

F. Abuse Liability

FDA properly includes information on abuse liability as part of “health risk” information. As FDA notes, abuse liability indicates the degree to which users of a product are likely to become addicted. 84 Fed. Reg. 50604. FDA also notes that such information “may provide insight into the use and adoption of the product, which is an important part of FDA’s assessment of the health risks of the new tobacco product as part of its determination of the risks and benefits to the population as a whole.” 84 Fed. Reg. at 50604. In this connection, however, FDA’s passing reference to the fact that “real world, actual use data may provide outcomes relevant to the products’ abuse liability, including misuse,” (84 Fed. Reg. at 50604) is an inadequate recognition of the extensive data that should be available from real-world experience. FDA should reasonably expect manufacturers whose products have been widely used for many years to have substantial data on the abuse liability of their products. Where substantial real-world evidence should have been collected by manufacturers, the absence of such evidence in an application should be decisive. As FDA notes, “abuse liability is an important part of FDA’s finding of whether permitting the marketing of the new tobacco product would be APPH.” 84 Fed. Reg. at 50604.

Measurement of the amount of nicotine in the e-liquid is important but it is only one of many factors affecting the potency with which nicotine is delivered to the user. In recent years,

found that just “7.8% of respondents reported that they tried to quit smoking by switching to chewing tobacco, snuff, or snus; an additional 5.8% considered it but never tried, and most never considered it.” [Popova, L & Ling, PM, “Alternative Tobacco Product Use and Smoking Cessation: A National Study,” *American Journal of Public Health* 103(5):923-930, May 2013, <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3661190/pdf/nihms456593.pdf>.]

the abuse liability of ENDS products has increased sharply due to the introduction of liquids containing protonated nicotine (nicotine salts), which provide a more potent delivery of nicotine to the user, and delivery devices capable of far higher levels of power that aerosolize much greater quantities of the liquid with each puff and therefore deliver more nicotine to the user with each puff. It is no coincidence that these developments have coincided with an epidemic of youth usage of ENDS products and far higher percentage of youth using ENDS products frequently than in prior years. Extensive scientific literature indicates that such products are highly addictive and have been major factors in producing the current epidemic of youth usage of ENDS products.⁵ The use of nicotine salts enabled Juul's products to deliver a more potent dose of nicotine with less irritation and was an important factor driving the popularity of Juul products with youth. The potency of nicotine delivery also greatly increased the abuse liability of Juul products and contributed to sharp increases in frequency of use among youth using ENDS products. According to data from the 2019 National Youth Tobacco Survey, 34.2 percent of high school students using ENDS products used them on 20 or more days out of the past 30, a substantial increase over prior years.⁶ A separate national survey found that nearly half (46%) of high school seniors and one-third of tenth graders who vape nicotine do so nearly every day.⁷ Thus, it is not only the nicotine content of the liquid but also the form in which the nicotine appears that affects abuse liability. FDA should establish a policy that would prevent the marketing of products that have the capability of delivering nicotine at such potent doses.

The proposed rule properly requires provision of information on how consumers actually use a product, including whether and how a consumer can change the product design and add or subtract ingredients and whether the consumer that allows users to change performance features such as temperature, voltage or wattage. 84 Fed. Reg. at 50597-98; §1114.7(i)(3). The ability of consumers to change the operation of the product can directly affect the delivery of nicotine and thus alter the abuse liability of a product.

Thus, even controlling for the presence of protonated nicotine would be insufficient to protect the public health against products with an unacceptably high potential for addicting youth. Nicotine delivery can also be affected by the temperature to which the liquid is heated, with higher temperatures yielding more potent delivery of nicotine, and the power settings, measured in watts, with more potent delivery of nicotine at higher power settings. For example,

⁵ Jackler, RK, Ramamurthi, D, "Nicotine arms race: JUUL and the high-nicotine product market," *Tobacco Control*, published online February 6, 2019. Office of the Surgeon General, "Surgeon General's Advisory on E-Cigarette Use Among Youth," December 18, 2018, <https://e-cigarettes.surgeongeneral.gov/documents/surgeon-generals-advisory-on-e-cigarette-use-among-youth-2018.pdf>.

⁶ Cullen, KA, et al., "e-Cigarette Use Among Youth in the United States, 2019," doi:10.1001/jama.2019.18387, published online November 5, 2019. See also, Wang, T, et al., "Tobacco Product Use and Associated Factors Among Middle and High School Students — United States, 2019," *Morbidity and Mortality Weekly Report (MMWR)* 68(12), December 6, 2019, <https://www.cdc.gov/mmwr/volumes/68/ss/pdfs/ss6812a1-H.pdf>.

⁷ Miech, R, et al., "Trends in Adolescent Vaping, 2017-2019," *New England Journal of Medicine*, published online September 18, 2019.

using low nicotine concentration liquid, so-called “third generation” e-cigarette devices were able to deliver nicotine to users at comparable levels as cigarettes, especially compared to previous generation devices.⁸ In recent years, the available wattage of ENDS systems has increased and the range of wattage has widened.⁹ Higher power levels deliver nicotine more effectively by aerosolizing much more liquid per puff.¹⁰ Consumers exposed to nicotine delivery from such high-powered devices absorb more nicotine and are therefore at risk of abuse liability.

The availability of open systems further complicates the regulatory task. Open systems enable consumers to introduce different liquids into different delivery devices. When consumers can introduce different nicotine liquids with different nicotine contents or with protonated rather than unprotonated nicotine, the consumers themselves are capable of increasing the abuse liability of the product. Moreover, open systems also enable consumers to modify the power settings so that the consumer can effectively control the nicotine delivery.¹¹ Studies have shown that increased wattage and heat also increase the health impact of these products. For example, one study showed that higher wattage heating coils, which increase temperature, also increase levels of formaldehyde and other volatile carbonyls.¹² Notably, consumers may not even understand what power device they are using and how the power of the device impacts nicotine delivery.¹³ It is difficult to evaluate if products are APPH for “typical” users when they are able to vary so many elements of their e-cigarette experience, from the e-liquid nicotine content and flavor to the device coil, battery, and size. Regulation that deals only with the nicotine content of the liquid or only with the power of the delivery device cannot effectively address the abuse liability of the product and cannot adequately protect the public health. Thus, in assessing the abuse liability of specific ENDS products, FDA must consider the extent to which the features of the product are subject to manipulation so as to make the potential for abuse unacceptable and thus inconsistent with the public health standard.

⁸ Wagener, TL, et al., “Have combustible cigarettes met their match? The nicotine delivery profiles and harmful constituent exposures of second-generation and third-generation electronic cigarette users,” *Tobacco Control* 26:e23-e28, 2017, <https://tobaccocontrol.bmj.com/content/tobaccocontrol/26/e1/e23.full.pdf>.

⁹ See, e.g., Vape Wild, “What Wattage Should You Vape At? How to Decide on Watts,” June 27, 2019, <https://www.vapewild.com/blog/what-wattage-should-you-vape-at-how-to-decide-on-watts/#>.

¹⁰ Talih, S, et al., “Effects of User Puff Topography, Device Voltage, and Liquid Nicotine Concentration on Electronic Cigarette Nicotine Yield: Measurements and Model Predictions,” *Nicotine & Tobacco Research* 17(2):150-7, 2015.

¹¹ Harvanko, AM, “Electronic Cigarette Liquid and Device Parameters and Aerosol Characteristics: A Survey of Regular Users,” *Addictive Behaviors* 84:201-206, 2018, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6580851/pdf/nihms-964336.pdf>. Talih, S, et al., “Effects of User Puff Topography, Device Voltage, and Liquid Nicotine Concentration on Electronic Cigarette Nicotine Yield: Measurements and Model Predictions,” *Nicotine & Tobacco Research* 17(2):150-7, 2015.

¹² Geiss, O, Bianchi, I, & Barrero-Moreno, J, “Correlation of volatile carbonyl yields emitted by e-cigarettes with the temperature of the heating coil and the perceived sensorial quality of the generated vapours,” *International Journal of Hygiene and Environmental Health* 219(3):268-277, 2016, <https://www.sciencedirect.com/science/article/pii/S1438463916000158>.

¹³ Rudy, AK, et al., “Assessing electronic cigarette effects and regulatory impact: Challenges with user self-reported device power,” *Drug and Alcohol Dependence* 179:337-340, 2017.

The combination of new formulations of nicotine capable of producing more potent delivery of nicotine and new delivery devices capable of greatly increasing the temperature of the aerosol and increasing the wattage of the device means that any regulatory program designed to limit the overall abuse liability of an ENDS product must account for the effects of multiple factors. Accordingly, FDA should consider granting applications only for products for which a scientifically appropriate ceiling on nicotine delivery can be shown to exist for the product as it has the potential to be used by consumers and denying applications for products for which no such showing is made.

G. Use Topography

Similarly, FDA correctly includes investigations of “how consumers actually use the product, including use topography, the product use frequency, use trends over time, and how such use affects the health risks of individual users” as “health risks” for which the provision of information is required. Sec. 114.7(k)(1)(ii)(B). FDA properly warns that it “may refuse to file a PMTA that does not contain substantive information” regarding these issues. 84 Fed. Reg. at 50605. FDA properly encourages the use of studies of actual use to develop such information.

FDA requires information on the principles of operation of products, including how the manufacturers expect a “typical consumer” to use their products and information such as the “length of time it takes for a user to consume a single unit of the product” 84 Fed. Reg. at 50596-50597. In addition, FDA requests data on “how consumers actually use the product, including use topography, the product use frequency, use trends over time, and how such use affects the health risks of the product to individual users.” 84 Fed. Reg. at 50604. FDA rightfully recognizes the difference between how the manufacturers expect and intend for consumers to use their products compared to how consumers actually use their products. For instance, consumers have been known to “direct drip” e-liquid onto e-cigarette device coils,¹⁴ mix their own e-cigarette liquid,¹⁵ and cigars are often modified to add marijuana to create “blunts.”¹⁶ These changes can affect users’ exposure to toxicants and impact the health risk profiles.

We recognize that there are many variables for e-cigarette use, including nicotine strength of the e-liquid, battery power, coil resistance, and user’s puffing habits. Research already shows that there is essentially no “typical user,” nor is there even a narrow range in

¹⁴ Talih, S, et al., “‘Direct Dripping’: A High-Temperature, High-Formaldehyde Emission Electronic Cigarette Use Method,” *Nicotine & Tobacco Research* 18(4):453-9, 2016, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6220833/pdf/ntv080.pdf>.

¹⁵ Davis, B, et al., “Nicotine Concentrations in Electronic Cigarette Refill and Do-It-Yourself Fluids,” *Nicotine & Tobacco Research* 17(2):134-41, 2015, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4892702/pdf/ntu080.pdf>.

¹⁶ Trapl, ES, et al., “Cigar Product Modification Among High School Youth,” *Nicotine & Tobacco Research* 20(3):370-376, 2018. Giovenco, D, et al., “‘They’re Pretty Much Made for Blunts’: Product Features That Facilitate Marijuana Use Among Young Adult Cigarillo Users in the United States,” *Nicotine & Tobacco Research* 19(11):1359-1364, 2017.

which to classify how users “typically” use e-cigarettes.¹⁷ Nevertheless, it is vital that FDA base its regulatory decisions on the way consumers actually use the product because it is actual use, not intended use, that determines the abuse liability and health risk presented by the product. Manufacturers whose products have already been on the market should already know how consumers are actually using their products given the length of time most products have already been on the market. An application from a manufacturer that has had a product on the market for years but failed to collect such information should not be granted.

H. Human Factors and Unintended Uses

Section 1114.7(k)(1)(v) requires production of information relevant to “human factors” that influence the health risks of the product, including use conditions, use environments, use related hazards, estimate use error risk, potential unintended uses, risk controls, and adverse experiences related to such uses. 84 Fed. Reg. at 50607. As with other areas of inquiry regarding health risks, the proposed rule states that if a PMTA does not contain a threshold amount of information, FDA intends to refuse to file the application and that if FDA lacks sufficient information to determine the potential risks and benefits of the product it intends to issue a no marketing order. *Id.*

The importance of evaluating potential unintended uses has been highlighted by the recent fatal outbreak of lung disease related at least in part to unintended uses of ENDS devices. Devices in which pods or other containers of liquid can be inserted are particularly vulnerable to misuse even if the manufacturer does not intend misuse to occur. In evaluating a PMTA for such delivery devices, FDA should evaluate the likelihood that a device can be misused in this manner. If devices in which pods or other containers of liquid can be inserted cannot be designed to eliminate such misuse FDA should consider restricting PMTAs to ENDS products that are completely closed, i.e., products in which it is not feasible for the consumer to vary the liquid that will be aerosolized.

As noted above, the fact that many new products that have been on the market for years will be the subject of PMTAs gives manufacturers the opportunity, and the obligation, to develop information on the way these products are actually being used. A manufacturer whose product has been on the market for years should have considerable evidence regarding actual use, and misuse, and no PMTA should be granted to a manufacturer who fails to provide that information.

I. Unintentional Ingestion

FDA requires the inclusion of information in an application describing the container closure system for the new tobacco product, including design features developed to prevent the risk of accidental exposure. §1114.7(i)(1)(vi). Such a requirement is necessary to eliminate

¹⁷ Harvanko, AM, et al., “Electronic Cigarette Liquid and Device Parameters and Aerosol Characteristics: A Survey of Regular Users,” *Addictive Behaviors* 84:201-206, 2018, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6580851/pdf/nihms-964336.pdf>.

unintentional exposures to nicotine, and it will be critical to ensure that such information is included in every application given the serious risks posed to children of unintentional nicotine ingestion or absorption through the skin. Child-resistant packaging is urgently needed for all e-cigarette and liquid nicotine products given the substance's serious negative health effects.

Liquid nicotine is extremely toxic and poses an urgent—yet preventable—poisoning threat, particularly to young children. Nicotine is extremely toxic and is not a benign substance. Exposure to even small amounts of nicotine can cause serious illness in children and can be fatal in higher doses. Liquid nicotine as used in e-cigarette products is particularly harmful because it can be easily absorbed into the body. E-cigarette liquid nicotine solutions are sold in highly concentrated solutions, and it is common to find liquid nicotine containing upwards of 36 milligrams of nicotine per milliliter of liquid. At this concentration, a small 15 mL dropper bottle of liquid nicotine would contain enough nicotine to kill four 10 kg children. Even a single teaspoon of liquid nicotine at this concentration could kill a small child.

In light of this serious concern, it is essential that e-cigarette and liquid nicotine devices “design out” the risk of unintended exposures among young children, and this is must be a serious consideration in the APPH determination. FDA must not authorize the marketing of any new tobacco product that does not incorporate appropriate child-resistant design features that prevent unintentional exposures, as such products inherently cannot be considered appropriate for the protection of public health.

J. Dual and Poly-Use

FDA also correctly includes investigations of dual and poly-use as aspects of health risk. Sec. 1114.7(k)(1)(C). It also identifies as aspects of health risk, investigations of the likelihood of whether current tobacco product users will start using the new tobacco product, whether they will use it exclusively or switch back to other tobacco products, and whether they will start or continue to use the product when they otherwise would have quit. Sec. 1114.7(k)(1)(D)-(F). This type of information is important because surveys find dual and poly-tobacco use prevalent among adults and youth.¹⁸ FDA properly warns applicants that if a PMTA does not contain a threshold amount of information on these issues FDA “intends to refuse to file the application.” FDA explicitly and correctly draws the link between provision of this information regarding “health risks” and its related ability “to determine the potential risks and benefit to the population as a whole” of granting an application and concludes that “if a PMTA lacks sufficient information needed for FDA to make these determinations, FDA intends to issue a no marketing

¹⁸ For instance, among adult e-cigarette users, 58.8% were current cigarette smokers [CDC, *Electronic Cigarettes: What's the Bottom Line?*, November 26, 2019, https://www.cdc.gov/tobacco/basic_information/e-cigarettes/about-e-cigarettes.html.] Among high school current tobacco users, 41.7% used two or more products [Wang, T, et al., “Tobacco Product Use and Associated Factors Among Middle and High School Students — United States, 2019,” *MMWR* 68(12), December 6, 2019, <https://www.cdc.gov/mmwr/volumes/68/ss/pdfs/ss6812a1-H.pdf>.]

order.” 84 Fed. Reg. at 50605. An application from a manufacturer that has had a product on the market for years but failed to collect such information should not be granted.

K. Bridging

The proposed rule permits an applicant to “choose to use data from a study conducted using a different tobacco product in an attempt to demonstrate the health risks of the products that is the subject of the application.” 84 Fed. Reg. at 50599. Although the discussion in the proposed rule lists several examples of where “bridging” may be appropriate, it does not establish clear criteria to identify instances where bridging may be permitted. FDA “recommends” that an applicant relying on bridging present “the rationale and justification to support the use of bridging studies” but does not identify the criteria FDA will use to evaluate the rationale. FDA should not grant an application based on “bridged” data unless FDA concludes that there is compelling evidence that the differences between data for the product that is the subject of the application and the data sought to be “bridged” would be immaterial to FDA’s resolution of the application. In any instance in which FDA relies on “bridged” information to support its grant of an application FDA should provide an explanation of why it did not require the applicant to present data directly about the product that is the subject of the application rather than relying on “bridged” data. The undersigned organizations are especially concerned with the inadequacy of using “bridged” data to inform FDA’s evaluation of the effect on youth of the granting of PMTA applications, and we address this issue in Part IV.A and B, *infra*.

IV. INFORMATION ABOUT THE POPULATION-WIDE EFFECTS OF THE PRODUCT

A. The likelihood that a product will increase use of tobacco products by current nonusers, including youth, is an essential element in determining whether the marketing of a product is APPH.

Section 1114.7(k)(1)(iii) requires reports “regarding the likelihood that consumers who have never used tobacco products, particularly youth and young adults, will initiate use of the tobacco product and the likelihood that consumers who have never used tobacco products and adopt use of the tobacco product will switch to other tobacco products that may present higher levels of individual health risk.” 84 Fed. Reg. at 50605. Given the epidemic of youth ENDS usage that has been thoroughly documented in numerous FDA statements and the recent release of the results from the 2019 National Youth Tobacco Survey, which shows that 5 million adolescents are currently using ENDS products, many of them on a frequent basis,¹⁹ provision of information on youth usage by the applicant pertaining to its specific product should be of

¹⁹ Cullen, KA, et al., “e-Cigarette Use Among Youth in the United States, 2019,” doi:10.1001/jama.2019.18387, published online November 5, 2019. See also, Wang, T, et al., “Tobacco Product Use and Associated Factors Among Middle and High School Students — United States, 2019,” *MMWR* 68(12), December 6, 2019, <https://www.cdc.gov/mmwr/volumes/68/ss/pdfs/ss6812a1-H.pdf>.

paramount importance. Many of the products that will be the subject of PMTA applications are likely to be the very products that have fueled this epidemic or products designed to simulate them, and FDA should hold applicants to a high standard in requiring evidence regarding youth usage of the product.

FDA properly notes that if the PMTA does not contain a threshold amount of information regarding the likelihood of uptake by current nonusers it intends to refuse to file the application. 84 Fed. Reg. at 50605. FDA should set this threshold at a high level. Given the level of the epidemic, manufacturers that have been selling ENDS products for more than three years have had ample opportunity to develop information about youth usage of their products. Manufacturers that have not done so should not be rewarded with the grant of an application. FDA correctly concludes that if FDA lacks information sufficient to determine the potential risks and benefit to the population as a whole it intends to issue a no marketing order for the new tobacco product. 84 Fed. Reg. at 50606. Indeed, with respect to Juul, the fact that its products are used by 60 percent of young people who use ENDS products places a special burden on the company to demonstrate that its products will not continue to be used by youth.

B. The proposed rule should be amended to require direct evidence of youth risk perception.

Although the proposed rule states that “FDA will need to understand how youth may use or intend to use the proposed product because youth are a population of particular concern for initiating tobacco use,” it does not require research to be conducted on youth. 84 Fed. Reg. at 50606. As the undersigned organizations have repeatedly emphasized in previous comments and letters,²⁰ any product application that FDA considers must include data on youth perception. Especially in light of current epidemic of e-cigarette use by adolescents, data on how adolescents perceive the product and its marketing, and how adolescents’ risk perception would affect the level of youth use, are vital to allow FDA to assess the likelihood of initiation of product use by young people and if the product is appropriate for the protection of public health. In numerous places in the rule, FDA acknowledges the importance of risk perception and its relationship to

²⁰ Letter from Tobacco-Free Kids and Five Public Health Groups, Re: Necessity of adolescent risk perception data in Modified Risk Tobacco Applications, February 15, 2019. Letter from Tobacco-Free Kids and Five Public Health Groups, Re: Marketing order for IQOS, May 14, 2019. Comments of Tobacco-Free Kids, et al., in Docket No. Docket No. FDA-2017-D-3001, February 11, 2019, re: Modified Risk Tobacco Product Applications for IQOS system with Marlboro HeatSticks, IQOS system with Marlboro Smooth Menthol HeatSticks, and IQOS system with Marlboro Fresh Menthol HeatSticks submitted by Philip Morris Products, S.A. Comments of Tobacco-Free Kids, in Docket No. FDA-2018-N-3261, January 22, 2019, re: Tobacco Products Scientific Advisory Committee; Notice of Meeting re Altria/U.S. Smokeless Tobacco Company’s Modified Risk Application for Copenhagen Snuff Fine Cut. Comments of Tobacco-Free Kids, in Docket No. FDA-2014-N-1051, January 22, 2019, re: Tobacco Products Scientific Advisory Committee meeting on amendments to Modified Risk Tobacco Product Applications for Snus Products Submitted by Swedish Match North America Inc. Comments of Tobacco-Free Kids, in Docket No. FDA-2018-N-3504, December 7, 2018, re: Tobacco Product Application Review; Public Meeting; Request for Comments. Comments of Tobacco-Free Kids, in Docket No. FDA-2018-N-2066, August 29, 2018, re: Tobacco Products Scientific Advisory Committee; Notice of Meeting re R.J. Reynolds Modified Risk Applications for Camel Snus.

tobacco use behavior, but despite these acknowledgments FDA fails to require data from studies that directly measure adolescent risk perception.

Adolescents process information, make decisions and respond to stimuli in ways that are different from adults, including young adults. For decades, we have known that virtually all new tobacco users begin as an adolescent or younger, that tobacco industry marketing has been targeted to take advantage of how young people make decisions and perceive risk, and that it is essential to understand how youth perceive different messages and products to understand how they will behave. As the adolescent population consists of both users and non-users of the tobacco products currently available on the market, FDA must consider whether the introduction of new products or allowing certain products to stay on the market would reinforce continued use by existing youth users, encourage initiation among non-users, or relapse among former users.

Though much of the FDA's guidances on youth perception data are related to modified tobacco risk product applications, it is clear that the agency believes that data on youth perception are important generally and is willing to work with companies to design studies that yield relevant information within appropriate ethical guidelines to ensure that the studies themselves do not create interest in tobacco products by youth. Thus, in addition to the section included in this proposed rule (84 Fed. Reg. at 50605-50606), in its Draft Guidance for PMTAs for ENDS, FDA cites the importance of evaluations of the likelihood of initiation among never-users and former users of tobacco products, including "*scientific information on the likelihood of product use by youth, young adults, pregnant women and other vulnerable populations.*"²¹ (emphasis added.)

As the FDA Draft Guidance for the preparation of MRTP applications makes clear, FDA requires only that "all study subjects *receiving tobacco products* are current daily tobacco product users at least 21 years of age."²² Not only is this limitation not applicable to studies of promotional material to determine the effect of such materials on adolescent risk perception or interest in using the product, but the FDA Guidance states that inclusion of the effect on adolescent perception should be an essential features of such studies. The Guidance states:

To address the effect of the MRTP on tobacco use initiation, FDA recommends that applicants submit:

- Human studies that evaluate consumer perception of the product, including its labeling, marketing and advertising.

These studies should be designed to provide evidence regarding the likelihood of population benefit or harm from the proposed product, including:

²¹ FDA Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems Guidance for Industry, Draft Guidance (May 2016), at 36 (emphasis added).

²² FDA Draft Guidance, Modified Risk Tobacco Applications (March 2012), at 29 (emphasis added).

- The likelihood that consumers who have never used tobacco products, particularly youth and young adults, will initiate use of the tobacco product;²³

Although research among non-smokers, and non-smoking youth in particular, requires care, researchers have been studying youth perception of tobacco products and marketing for decades, and protocols are available that would enable applicants to gather the necessary information to provide to FDA. The proposed rule provides some parameters for conducting research with minors (84 Fed. Reg. at 50606), and FDA’s guidance on MRTP offered applicants an opportunity to work with the agency to determine the best way to conduct studies involving youth:

When designing consumer perception studies, applicants should take care that the studies themselves do not promote use of the product, particularly among vulnerable populations, such as youth, non-users of tobacco products, and pregnant women. FDA recommends that applicants meet with FDA to discuss research plans before embarking on research with vulnerable populations. Section IX.B of this guidance provides information on requesting a meeting with FDA.²⁴

These procedures are consistent with the recommendations made by the Institute of Medicine’s (IOM) 2012 report, *Scientific Standards for Studies on Modified Risk Tobacco*, which stated that “FDA should require studies to include populations of special relevance, including (but are not limited to). . . adolescents”²⁵ and included an assessment of the effects on youth as “an essential element in establishing the public health benefit of an MRTP.”²⁶ The IOM report detailed ideas for how research on youth perceptions of risk of MRTPs can be conducted consistent with ethical standards.²⁷ For example, IOM suggests that such research could be appropriately done under the supervision of an independent third party.²⁸ Such a procedure would make it possible for an applicant to develop evidence regarding the effect of the marketing of a product on this population. IOM noted that “Survey research or perception/messaging research among non-smokers is acceptable where the non-smokers are not being exposed to the product.”²⁹ Even in the case of studies that include exposure to a particular tobacco product among non-users (which is not critical in this case), IOM concluded, “Experimental research that exposes non-users to products is ethically problematic; but such research cannot completely be ruled out because it could provide critically valuable information. The ethics, risks, and benefits need to be determined on a case by case basis.”³⁰

Despite its recognition that these procedures make it possible to survey youth populations regarding risk perception and the effect of tobacco product marketing, FDA has not required

²³ *Id.* at 20 (emphasis added).

²⁴ FDA, Draft Guidance, Modified Risk Tobacco Applications, March 2012, at 26.

²⁵ IOM Report at 14.

²⁶ *Id.* at 50.

²⁷ *Id.* at 10.

²⁸ *Id.* at 57.

²⁹ *Id.* at 52.

³⁰ *Id.* at 52-53.

provision of such information. The failure to require such evidence will make FDA’s estimates of these important factors less accurate and result in exposing many more young people to marketing messages that might otherwise have been prevented.

FDA has suggested that bridging information could be sufficient to evaluate the impact of the product and product marketing on youth behavior. 84 Fed. Reg. at 50606. However, bridging information that is “extrapolated from young adults” or references foreign data may be insufficient to show how youth in the U.S. will perceive and use such products. For instance, FDA’s own social scientists concluded that the premarket application for Philip Morris International’s IQOS and Heatsticks did not provide sufficient information on youth.³¹ In reference to the studies that oversampled 18-25 year olds to supposedly represent youth, the FDA scientists noted, “the applicant did not submit any information or bridging study data to youth under age 18” and “the applicant did not include bridging information on youth use of other products (e.g., cigarettes, e-cigarettes). This might have helped FDA better understand youth intentions and perceptions with respect to IQOS.”³² In response to the studies from Japan and Italy that PMI submitted, the FDA scientists stated, “These studies, while providing an indication of intent among smokers, nonsmokers, and former smokers, cannot be considered as absolute indicators of behaviors when/if IQOS is a marketed product.”³³ These two countries have different cultures, different marketing rules and different regulatory circumstances. There was no meaningful data or analysis to demonstrate the applicability of the limited experience in those countries to the American setting, and yet the Technical Project Lead of the Office of Science overruled those concerns³⁴ and a PMTA was granted by FDA.

The use of bridging data from other age groups and from foreign populations provides an inadequate basis for reaching conclusions about risk perceptions among youth in the United States. The undersigned organizations believe that reliance on bridging data from other age groups or foreign countries should be not a sufficient basis for granting a PMTA and that the proposed rule should be changed to require scientific information regarding risk perception to be gathered directly from U.S. adolescent populations, particularly in situations where the product has already been on the market for years.

C. There is overwhelming evidence that flavored tobacco products have fueled the youth epidemic of e-cigarette and other tobacco product use and FDA should take account of this evidence in evaluating PMTAs for flavored products.

Provision of information regarding the flavor additives in and marketing of flavored tobacco products is particularly important. Numerous studies have demonstrated that the

³¹ FDA, Technical Project Lead Review for PMI heated tobacco products (April 29, 2019), at 83.

³² *Id.* at 75.

³³ *Id.* at 76.

³⁴ *Id.* at 83.

overwhelming majority of youth users use flavored products, especially mint and menthol, while data about the effectiveness of flavorings in products for adults to quit smoking is still lacking.

1. Flavored tobacco products attract youth.

FDA recognizes that flavored tobacco products, which have proliferated in recent years, play a critical role in attracting new tobacco users and increase the likelihood of long-term addiction.³⁵ The widespread availability of flavored non-cigarette tobacco products and use of these products among youth presents a public health risk. Flavors increase the attractiveness of tobacco products to young people and are being introduced into the marketplace with no regard for their impact on youth. The young people who are lured to use tobacco products because of these flavors thus expose themselves to the risk of a lifetime of addiction. For these reasons it is crucial that FDA evaluate flavored products individually, rigorously and critically.

FDA has long recognized the potential for flavored products to increase youth initiation of tobacco use. When FDA submitted the deeming rule to OIRA for review in 2016, it recommended prohibiting the marketing of flavored e-cigarettes, cigars and hookah in the absence of an FDA marketing order and provided 17 pages of text summarizing the strong scientific data supporting this recommendation.³⁶ This recommendation was deleted by OIRA; as a result flavored ENDS, cigars, and hookah products have remained on the market since 2016 and the epidemic increase in youth usage of ENDS products ensued. Moreover, FDA has recently documented the effect of flavors in fueling youth usage of cigars and has proposed regulatory measures to deal with it.³⁷

The presence of flavors in ENDS products has fueled the epidemic of youth e-cigarette use. Tobacco companies market ENDS products in many flavors that appeal to youth, such as gummy bear, berry blend, chocolate, peach, cotton candy, strawberry, grape, mint and menthol. In fact, the *same* flavor chemicals used in flavored cigars and smokeless tobacco products are also used in candy and drink products popular with kids such as LifeSavers, Jolly Ranchers and Kool-Aid.³⁸ As of 2017, researchers had identified more than 15,500 unique e-cigarette flavors available online. The 2016 Surgeon General Report on e-cigarettes concluded, “E-cigarettes are marketed by promoting flavors and using a wide variety of media channels and approaches that have been used in the past for marketing conventional tobacco products to youth and young adults.”³⁹ Thus far none of these flavors have been evaluated by any scientific agency for their safety related to

³⁵ 83 Fed. Reg. at 12295-96.

³⁶ Deeming Final Rule Redline Changes in Docket No. FDA-2014-N-0189-83193, Deeming Tobacco Products to be Subject to the Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Regulations on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products, May 27, 2016, <https://www.regulations.gov/document?D=FDA-2014-N-0189-83193>.

³⁷ FDA’s March 12, 2019 Guidance stated, “beginning 30 days after issuance of a final guidance, FDA will prioritize enforcement actions with respect to flavored cigars (other than tobacco flavors) that were on the market on August 8, 2016 and that meet the definition of New Tobacco Products.”

³⁸ Brown, JE, et al., “Candy Flavorings in Tobacco,” *New England Journal of Medicine*, 370: 2250-2252, 2014.

³⁹ HHS, *E-Cigarette Use Among Youth and Young Adults. A Report of the Surgeon General*. Atlanta, GA: HHS, CDC, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2016.

regular use or their effectiveness in helping smokers quit, yet it is clear that many of these flavors are appealing to youth.

The combined effects of the flavors themselves and their marketing have proved an attractive mix for youth. Research shows that no matter what the tobacco product, flavors appeal to youth and young adults. As summarized in FDA’s ANPRM on regulating flavors in tobacco products, data from the government’s 2013-2014 Population Assessment of Tobacco and Health (PATH) study found that 80.8 percent of 12-17 year olds who had ever used a tobacco product initiated tobacco use with a flavored product and 79.8 percent of current tobacco users had used a flavored tobacco product in the past month. Moreover, for each tobacco product, at least two-thirds of youth report using these products “because they come in flavors I like.”⁴⁰ Another national study found that 18.5 percent of young adult tobacco users (18-34 years old) currently use a flavored tobacco product, with younger age being a predictor of flavored tobacco product use. In fact, the study found that those aged 18-24 years old had an 89 percent increased odds of using a flavored tobacco product compared to those aged 25-34 years old.⁴¹

The data confirms that flavors play a major role in youth initiation and continued use of e-cigarettes. The 2016 Surgeon General Report on e-cigarettes concluded that flavors are among the most commonly cited reasons for using e-cigarettes among youth and young adults.⁴² Data from the 2016-2017 wave of the government’s Population Assessment of Tobacco and Health (PATH) study found that 70.3 percent of current youth e-cigarette users say they use e-cigarettes “because they come in flavors I like.”⁴³ The PATH study also found that 97 percent of current youth e-cigarette users had used a flavored e-cigarette in the past month.⁴⁴

FDA must take into consideration these youth usage patterns when evaluating applications for marketing flavored tobacco products. Given that most of the tobacco products subject to this proposed rule that FDA will be evaluating have been on the market for years, each applicant should be expected to provide data on usage, including among youth, for its products.

2. Mint vs. Menthol Flavoring in ENDS Products

The recent debate about the difference between mint and menthol e-cigarettes raises important issues that FDA needs to address. The urgency of this issue is clear: mint or menthol e-cigarette use among high school current e-cigarette users increased from 38.1 percent in 2018 to

⁴⁰ 83 Fed. Reg. 12296, citing 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.

⁴¹ Villanti, AC, et al., “Flavored Tobacco Product Use Among U.S. Young Adults,” *American Journal of Preventive Medicine* 44(4):388-391, 2013.

⁴² HHS, *E-Cigarette Use Among Youth and Young Adults. A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2016.

⁴³ FDA, *Modifications to Compliance Policy for Certain Deemed Products: Guidance for Industry, Draft Guidance*, at 9, March 13, 2019, <https://www.fda.gov/media/121384/download>.

⁴⁴ *Id.*

57.3 percent in 2019.⁴⁵ An estimated 1.2 million youth currently use mint or menthol flavored e-cigarettes.⁴⁶

The leading e-cigarette manufacturer, Juul, has been on record stating that its mint flavor “is a menthol-based flavor.”⁴⁷ Independent chemical analysis found that Juul’s Classic Menthol and Cool Mint flavors contained similar levels of menthol in the aerosol.⁴⁸ Data from the Monitoring the Future survey show that mint was by far the most popular flavor among 10th and 12th grade Juul users, and, more alarmingly, mint was more popular among more frequent e-cigarette users in 8th, 10th, and 12th grades.⁴⁹ If Juul’s mint is a menthol flavor and youth have such a strong preference for it, then the available data do not support allowing menthol or menthol-based flavors on the market. A preliminary, unpublished Truth Initiative analysis of Nielsen sales data from November of 2014 through September of 2019 shows that when Juul stopped selling other flavor versions of its products in convenience and other stores, sales of mint and menthol products sky-rocketed. These data suggest that consumers, especially youth, will use whatever flavor is available to them, a conclusion that further supports a prohibition on allowing menthol or menthol-based flavors on the market.

Each flavored product should be evaluated separately as part of the PMTA process. If there really is a difference between mint products and menthol products that justifies a difference in regulation, then applicants must show that such a difference exists, both in terms of chemical analysis, perceptions, and use patterns among smokers, e-cigarette users, and non-users, especially youth and other populations with a history of disproportionate menthol cigarette use.

3. FDA should not grant PMTAs for any flavored ENDS products in the absence of scientific data demonstrating that a particular flavor is necessary to help adult smokers quit, that such flavors would not increase tobacco product initiation by nonusers, and that the flavor itself does not increase the toxicity of the product.

Some ENDS products manufacturers have contended that permitting flavored ENDS products to be marketed is necessary to enable adult current smokers to switch entirely to the new product and that the benefits of flavored ENDS products outweigh the dangers they present to youth. There is little evidence, however, that ENDS products have enabled a large number of

⁴⁵ Cullen, KA, et al., “e-Cigarette Use Among Youth in the United States, 2019,” *JAMA*, published online November 5, 2019.

⁴⁶ Cullen, KA, et al., “e-Cigarette Use Among Youth in the United States, 2019,” *JAMA*, published online November 5, 2019.

⁴⁷ Testimony by James Monsees at House Committee on Oversight and Reform Hearing, July 25, 2019.

⁴⁸ Erythropel, HC, et al., “Flavorant–Solvent Reaction Products and Menthol in JUUL E-Cigarettes and Aerosol,” *American Journal of Preventive Medicine* 57(3):425-427, 2019.

⁴⁹ Leventhal, AM, et al., “Flavors of e-Cigarettes Used by Youths in the United States,” *Journal of the American Medical Association*, published online November 5, 2019.

adult current smokers to switch completely and even less evidence that flavors enhance the likelihood of their doing so.

No flavored ENDS product has been authorized or even reviewed for smoking cessation purposes by FDA. Public health authorities in the U.S. have found that there is not enough evidence to recommend e-cigarettes for tobacco cessation. In its ANPRM on regulating flavors in tobacco products, FDA referenced the National Academies of Sciences, Engineering, and Medicine report that found “limited evidence that e-cigarettes may be effective aids to promote smoking cessation,” and “moderate evidence from observational studies that more frequent use of e-cigarettes is associated with increased likelihood of cessation.” FDA then stated, “thus, the evidence remains inconclusive.”⁵⁰

Applicants may refer to adult preference for flavored e-cigarettes as evidence that adults need flavored e-cigarettes to quit smoking, but there have been no randomized controlled trials comparing the cessation efficacy of flavored vs. non-flavored or tobacco-flavored e-cigarettes. Further, FDA must look at the evidence available for each specific flavor being proposed, not flavored products as a category. A 2018 systematic review of 66 articles published on consumer preference for e-cigarettes found inconclusive evidence as to whether flavored e-cigarettes assisted smoking cessation.⁵¹

For example, claims that menthol e-cigarettes should remain on the market to provide a non-combusted alternative for menthol cigarette smokers should not be accepted without evidence demonstrating that menthol cigarette smokers would actually switch completely to menthol e-cigarettes and would not switch completely without the menthol flavoring. Moreover, any benefits resulting from such switching would have to be weighed against the risk of increased tobacco product initiation by nonusers resulting from the availability of these products.

Moreover, even if flavors were shown to increase the potential for flavors to promote complete switching by current smokers, such a benefit would have to be weighed against the potential for increasing initiation by nonusers. FDA should require manufacturers of flavored ENDS products to demonstrate not only that the benefits of the specific flavored product in promoting complete switching by current smokers outweigh the harms cause by increases in initiation by nonusers, but also that neither the product itself without the flavor nor other available alternatives could provide the same benefit at a lower cost to public health.

In addition, harmful chemicals or toxins have been identified in the additives used to flavor some products. Products that contain flavors that increase the toxicity of the product should not be granted a marketing order.

⁵⁰ 83 Fed. Reg. at 12298.

⁵¹ Zare, S, et al., “A systematic review of consumer preference for e-cigarette attributes: Flavor, nicotine strength, and type,” *PLoS One*13(3):e0194145, doi: 10.1371/journal.pone.0194145, 2018.

4. Flavored Cigars, Hookah, and Smokeless Products

Similarly, flavored cigars, smokeless tobacco and hookah are marketed in ways that make them attractive to kids. As detailed in previous comments by the undersigned groups on FDA's Advance Notice of Proposed Rulemaking (ANPRM) on regulation of flavors in tobacco products,⁵² there has been explosive growth in flavor options for cigars, such as candy, fruit, chocolate and various other flavors that appeal to youth that are sold in shiny, colorful packages, placed where kids can easily see them, and are priced much cheaper than cigarettes. In 2015, flavored products made up more than half of all smokeless tobacco sales, and menthol and mint flavors were by far the most popular.⁵³ Hookah tobacco also comes in a wide variety of flavors that appeal to youth. An industry publication stated, "While different cigars target a variety of markets, all flavored tobacco products tend to appeal primarily to younger consumers."⁵⁴ In its March 2019 guidance, FDA concluded that flavored cigars provide "no public benefit."⁵⁵ In light of the appeal of flavored cigars to young people, and the absence of any public health benefit from such products, there is no justification for the grant of a PMTA for flavored cigars.

The 2016-2017 wave of the PATH study found that 56.8 percent of 12-17 year olds who had ever smoked cigarillos started with a flavored product.⁵⁶ Older data from the 2014-2015 wave of the PATH study, which assessed use of all cigar types, found that 53.7 percent of current youth cigar smokers had used a flavored product in the last month.⁵⁷ In 2013-2014, 73.8 percent of youth cigar smokers reported that they smoked cigars "because they come in flavors I like."⁵⁸ Youth and young adults prefer brands that come in a variety of flavors, and that preference declines significantly with age – in one study, 95 percent of 12-17 year old cigar smokers reported a usual brand that makes flavored cigars compared with 63 percent of cigar smokers aged 35 and older.⁵⁹

Although cigarette smoking among youth in the U.S. has declined rapidly since the Tobacco Control Act went into effect, use of smokeless tobacco among youth has not followed that same trend, and among boys the prevalence of smokeless tobacco use is comparable to that of

⁵² Comments of Tobacco-Free Kids, et al., in Docket No. FDA-2017-N- 6565, July 19, 2018 re: Regulation of Flavors in Tobacco Products, Advance notice of proposed rulemaking.

⁵³ Kuiper, NM, et al., "Trends in sales of flavored and menthol tobacco products in the United States during 2011-2015," *Nicotine & Tobacco Research*, published online June 1, 2017.

⁵⁴ Niksic, M, "Flavored Smokes: Mmmmm...More Profits?" *Tobacco Retailer*, April 2007.

⁵⁵ FDA, "Modifications to Compliance Policy for Certain Deemed Products: Guidance for Industry, Draft Guidance," March 13, 2019, <https://www.fda.gov/media/121384/download>, at 16.

⁵⁶ *Id.*

⁵⁷ Rose, S, et al., "Flavour types used by youth and adult tobacco users in wave 2 of the Population Assessment of Tobacco and Health (PATH) Study 2015-2015," *Tobacco Control*, published online September 21, 2019.

⁵⁸ 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.

⁵⁹ Delnevo, C, et al., "Preference for flavoured cigar brands among youth, young adults and adults in the USA," *Tobacco Control* 24(4):389-94, 2015.

cigarettes (8.4% vs. 8.8%).⁶⁰ Tobacco industry documents indicate that smokeless tobacco companies knew that “sweeter milder flavours could increase appeal to starters by potentially lowering the pH of tobacco.”⁶¹ In particular, mint flavoring plays an important role in smokeless tobacco use initiation and dependence, by making the product more tolerable to new users.⁶² The 2014-2015 PATH study found that 62.7 percent of current youth smokeless tobacco users had used a flavored product in the last month.⁶³ The 2013-2014 PATH study found that 68.9 percent of 12-17 year olds who had ever used smokeless tobacco used flavored smokeless tobacco the first time they tried the product.⁶⁴ Separately, the 2019 NYTS found that 48 percent of middle and high school smokeless tobacco users had used flavored smokeless tobacco in the past month.⁶⁵

Moreover, no smokeless tobacco products, including flavored products, have been shown to effectively help smokers quit. The 2008 Update of the U.S. Public Health Service Clinical Practice Guidelines regarding tobacco cessation concluded, “the use of smokeless tobacco products is not a safe alternative to smoking, nor is there evidence to suggest that it is effective in helping smokers quit.”⁶⁶ Evidence in the U.S. does not indicate that smokers would switch to exclusive smokeless tobacco use (i.e., the evidence does not demonstrate that smokers who take up smokeless tobacco would abstain from smoking cigarettes). U.S. smokers do not prefer to use smokeless tobacco to quit smoking. A recent study showed that daily smokers were no more likely to stop smoking for seven days with Camel snus compared to FDA-approved nicotine gum. The study authors stated, “Snus (with levels of nicotine similar to nicotine gum) was no better than nicotine gum in sustaining abstinence from smoking, but was significantly more toxic.”⁶⁷ Older data on smokers’ attitudes about switching to smokeless tobacco confirm this finding.⁶⁸

⁶⁰ CDC, “Vital Signs: Tobacco Product Use Among Middle and High School Students — United States, 2011–2018,” *MMWR* 68(6):157-164, February 15, 2019, <https://www.cdc.gov/mmwr/volumes/68/wr/pdfs/mm6806e1-H.pdf>. CDC, “Tobacco Use Among Middle and High School Students—United States, 2000-2009,” *MMWR* 59(33):1063-1068, <https://www.cdc.gov/mmwr/pdf/wk/mm5933.pdf>.

⁶¹ Kostygina, G & Ling, PM, “Tobacco industry use of flavourings to promote smokeless tobacco products,” *Tobacco Control* 25(Suppl 2):ii40-ii49, November 2016.

⁶² Kostygina, G & Ling, PM, 2016.

⁶³ Rose, S, et al., “Flavour types used by youth and adult tobacco users in wave 2 of the Population Assessment of Tobacco and Health (PATH) Study 2015-2015,” *Tobacco Control*, published online September 21, 2019.

⁶⁴ 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.

⁶⁵ Wang, T, et al., “Tobacco Product Use and Associated Factors Among Middle and High School Students — United States, 2019,” *MMWR* 68(12), December 6, 2019, <https://www.cdc.gov/mmwr/volumes/68/ss/pdfs/ss6812a1-H.pdf>.

⁶⁶ Fiore, MC, et al., *Treating Tobacco Use and Dependence: 2008 Update, U.S. Public Health Service Clinical Practice Guideline*, May 2008, http://www.surgeongeneral.gov/tobacco/treating_tobacco_use08.pdf.

⁶⁷ Berman, ML, et al., “Consortium on Methods Evaluating Tobacco: Research Tools to Inform FDA Regulation of Snus,” *Nicotine & Tobacco Research* [Epub ahead of print], doi: 10.1093/ntr/ntx228, October 4, 2017, <https://academic.oup.com/ntr/advance-article-abstract/doi/10.1093/ntr/ntx228/4331541>.

⁶⁸ A 2009 study based on data from the California Tobacco Survey showed that the majority of daily smokers were not interested in switching their cigarettes for smokeless tobacco. In fact, 87 percent of smokers said they were “definitely not” or “probably not” open to the idea of replacing their cigarettes with smokeless tobacco, compared to only 12.7 percent of the smokers who reported that they “definitely” or “probably” would consider it. [Timberlake, D, “Are smokers receptive to using smokeless tobacco as a substitute?” *Preventive Medicine* 49(2-3):229-32, 2009, <http://www.ncbi.nlm.nih.gov/pubmed/19631684>.] A national cross-sectional study of current and former smokers

Thus, given their appeal to youth, in the absence of compelling evidence that they help smokers quit, there is no justification for granting a PMTA for flavored smokeless tobacco products.

D. Effect on Vulnerable Populations

Tobacco products are targeted to appeal to different demographic groups. In considering PMTAs, FDA should consider both the effect of granting a marketing order on the general population but should also consider whether the product will have a disproportionate impact on any particular demographic or regional group. The proposed rule fails to address the impact of a PMTA application on any vulnerable population and thus may result in FDA actions that have a disproportionate effect in certain markets or regions.

The United States has made enormous progress in reducing cigarette smoking. In the 50 years since the first Surgeon General’s report on smoking and health, the adult smoking rate has been cut by more than half.⁶⁹ Despite this progress, tobacco use remains the nation’s number one cause of preventable death,⁷⁰ and some populations within the U.S. experience a disproportionate health and economic burden from tobacco use. If we are to continue to make progress in reducing tobacco use and its toll, it is vital to identify and reach those populations most impacted. Therefore, it is essential to require applicants to demonstrate that the introduction of their products will have a beneficial health impact on the populations that are disproportionately impacted by tobacco. The fact that most of the data we have on these disproportionate effects relates to cigarette smoking only emphasizes the need for FDA to require provision of data on how the availability of ENDS products affects vulnerable populations. An examination of the data on cigarette smoking reveals just how disproportionate such effects can be.

Cigarette smoking has become more and more concentrated among certain population subgroups. Due to a range of factors, including the tobacco industry’s targeted marketing efforts, lower-income and less educated populations, certain racial and ethnic groups, geographic regions, lesbian/gay/bisexual communities as well as those suffering from mental illness are particularly burdened by tobacco use. Groups most impacted by the tobacco epidemic have consistently been

found that just “7.8% of respondents reported that they tried to quit smoking by switching to chewing tobacco, snuff, or snus; an additional 5.8% considered it but never tried, and most never considered it.” [Popova, L & Ling, PM, “Alternative Tobacco Product Use and Smoking Cessation: A National Study,” *American Journal of Public Health* 103(5):923-930, May 2013, <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3661190/pdf/nihms456593.pdf>.]

⁶⁹ Xu, X et al., “Annual Healthcare Spending Attributable to Cigarette Smoking: An Update,” *Am J Prev Med*, 2014. HHS, *The Health Consequences of Smoking – 50 Years of Progress A Report of the Surgeon General*, 2014.

⁷⁰ HHS, *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General*, 2014, <http://www.surgeongeneral.gov/library/reports/50-years-of-progress/>. See also, HHS, *Let’s Make the Next Generation Tobacco-Free: Your Guide to the 50th Anniversary Surgeon General’s Report on Smoking and Health*, Consumer Booklet, 2014.

targets of tobacco industry marketing. Disparities in smoking rates is a major contributor to the growing gap in health status and life expectancy between the rich and the poor in the U.S.^{71, 72}

1. Socioeconomic Status

Cigarette smoking has become ever more concentrated among populations with lower incomes and fewer years of education. More than one in five (21.3%) of adults with a household income less than \$35,000 smoke, compared to 13.3 percent of adults with a household income between \$75,000 and \$100,000, and 7.3 percent of those with a household income of \$100,000 or more.⁷³ Smoking rates among the uninsured and those with Medicaid (23.9% among each group) are more than double that of those with private health insurance coverage (10.5%).⁷⁴ Smoking prevalence is highest among adults with a GED (36%) and lowest among those with a graduate degree (3.7%). The smoking rate among college graduates is 7.1 percent.⁷⁵

2. Geographic Region

The burden of tobacco use also varies by geographic region. Smoking rates are highest among adults living in the Midwest and the South (16.2% and 14.8%, respectively) compared to the Northeast and West (12.5% and 10.7%, respectively).⁷⁶

According to a Truth Initiative report, Tobacco Nation is a group of thirteen states⁷⁷ that have consistently ranked in the top 25 percent of tobacco using states since 2011, stretching from the upper Midwest to the South. Adults living in Tobacco Nation are more likely to smoke than adults in the rest of the United States (21% vs. 15%), and they smoke more cigarettes per capita (59.2 packs vs. 31.1 packs).⁷⁸ Smokeless tobacco use among high school boys exceeded the

⁷¹ Bosworth, B, et al., *Later Retirement, Inequality in Old Age, and the Growing Gap in Longevity between Rich and Poor*, Brookings Institution, February 2016, <http://www.brookings.edu/research/reports2/2016/02/life-expectancy-gaps-promise-social-security>.

⁷² Ho, J & Fenelon, A, “The Contribution of Smoking to Educational Gradients in U.S. Life Expectancy,” *Journal of Health and Social Behavior* 56(3), 2015.

⁷³ U.S. Centers for Disease Control and Prevention (CDC), “Tobacco Product Use and Cessation Indicators Among Adults—United States, 2018,” *MMWR* 68(45):1013-1019, November 15, 2019, https://www.cdc.gov/mmwr/volumes/68/wr/mm6845a2.htm?s_cid=mm6845a2_w. Current smoking is defined as persons who reported having smoked ≥ 100 cigarettes during their lifetimes and, at the time of the survey, reported smoking every day or some days.

⁷⁴ CDC, “Tobacco Product Use and Cessation Indicators Among Adults—United States, 2018,” *MMWR* 68(45):1013-1019, November 15, 2019, https://www.cdc.gov/mmwr/volumes/68/wr/mm6845a2.htm?s_cid=mm6845a2_w.

⁷⁵ *Id.*

⁷⁶ *Id.*

⁷⁷ Alabama, Arkansas, Indiana, Kentucky, Louisiana, Michigan, Mississippi, Missouri, Ohio, Oklahoma, South Carolina, Tennessee and West Virginia.

⁷⁸ Truth Initiative, *Tobacco Nation: An Ongoing Crisis, 2019*, <https://truthinitiative.org/sites/default/files/media/files/2019/06/Tobacco-Nation-An-Ongoing-Crisis.pdf>.

national rate in 24 states, with the highest rates in the “Tobacco Nation” states of West Virginia (19.3%), Arkansas (17.9%), Kentucky (17.2%), Louisiana (15.8%), and Oklahoma (15.2%).⁷⁹

3. Race/Ethnicity

According to the 2018 National Health Interview Survey (NHIS), American Indians and Alaska Natives (AI/AN) are more likely than any other racial/ethnic subgroup to be current smokers, with a smoking rate of 22.6 percent. In comparison, 15 percent of Whites, 14.6 percent of African Americans and 9.8 percent of Hispanics smoke. Overall, 13.7 percent of U.S. adults are current smokers.⁸⁰

Despite initiating smoking later in life than whites, African-Americans smoking-caused disease burden and mortality is still significantly higher.⁸¹ One reason for this is that African-Americans quit smoking at lower rates, regardless of the age of initiation. As a result, African-Americans are at greater risk for remaining smoking throughout adulthood and this longer duration of smoking contributes to the higher disease burden.⁸²

4. Lesbian, Gay and Bisexual Communities

While analysis of sexual minority tobacco use has historically been excluded from state and national surveys, the 2018 NHIS found that 20.6 percent of lesbian, gay and bisexual (LGB) adults are current smokers, as compared to 13.5 percent of straight adults.⁸³ These disparities are due in large part to targeted marketing of LGBT populations by the tobacco industry.⁸⁴

⁷⁹ CDC, “Youth Risk Behavior Surveillance — United States, 2017,” *MMWR* 67(SS-8), June 15, 2018.

⁸⁰ CDC, “Tobacco Product Use and Cessation Indicators Among Adults—United States, 2018,” *MMWR* 68(45):1013-1019, November 15, 2019, https://www.cdc.gov/mmwr/volumes/68/wr/mm6845a2.htm?s_cid=mm6845a2_w.

⁸¹ HHS, “Tobacco Use Among US Racial/Ethnic Minority Groups—African Americans, American Indians and Alaskan Natives, Asian Americans and Pacific Islanders, and Hispanics: A Report of the Surgeon General,” 1998, http://www.cdc.gov/tobacco/data_statistics/sgr/1998/complete_report/pdfs/complete_report.pdf. See also, Roberts, ME, et al., “Understanding tobacco use onset among African Americans,” *Nicotine & Tobacco Research*, 18(S1): S49-S56, 2016; Alexander, LA, et al., “Why we must continue to investigate menthol’s role in the African American smoking paradox,” *Nicotine & Tobacco Research* 18(S1):S91-S101, 2016.

⁸² Roberts, ME, et al., “Understanding tobacco use onset among African Americans,” *Nicotine & Tobacco Research* 18(S1):S49-S56, 2016; Kulak, JA, et al., “Differences in Quit Attempts and Cigarette Smoking Abstinence Between Whites and African Americans in the United States: Literature Review and Results from the International Tobacco Control US Survey,” *Nicotine & Tobacco Research* 18(S1):S79-S87, 2016.

⁸³ CDC, “Tobacco Product Use and Cessation Indicators Among Adults—United States, 2018,” *MMWR* 68(45):1013-1019, November 15, 2019, https://www.cdc.gov/mmwr/volumes/68/wr/mm6845a2.htm?s_cid=mm6845a2_w.

⁸⁴ Stevens P, et al. “An analysis of tobacco industry marketing to lesbian, gay, bisexual, and transgender (LGBT) populations: strategies for mainstream tobacco control and prevention.” *Health Promotion Practice* 5(3 suppl):129S-134S, 2004.

5. Mental Illness and Psychological Distress

Adults with any mental illness have higher smoking rates.⁸⁵ Additional national data from the 2018 NHIS finds that 31.6 percent of adults with serious psychological distress are current smokers, compared to 13 percent of adults without serious psychological distress.⁸⁶ The tobacco industry has capitalized on this vulnerable population by marketing tobacco products as stress-reducing and developing relationships with homeless shelters and mental illness associations.⁸⁷

To appropriately address and eventually end the tobacco epidemic in America, more must be done to reduce tobacco-related disparities. FDA should require that applicants submit reports about use of their product by particularly vulnerable sub-populations. Since most of the products have been on the market for at least three years, manufacturers should already have much of this information. In addition, it is important for applicants to include target demographics, including populations identified as particularly vulnerable to tobacco use, as part of their marketing plans.

As drafted, the proposed requirements for PMTAs include a summary of the sales and distribution of the tobacco product, “to the extent that the applicant collects or receives such data.” 84 Fed. Reg. at 50622. This requirement would include demographic characteristics of product purchasers “such as age, gender, and tobacco use status.” 84 Fed. Reg. at 50623. These requirements alone are inadequate for FDA to assess the impact of the products on vulnerable populations.

It is critical to consider vulnerable populations because of their distinct experiences with tobacco products, including differences in marketing, pricing, product preferences, and use patterns. For instance, for decades, the tobacco industry has targeted certain populations to increase tobacco use rates, such as marketing menthol cigarettes to African-American communities. FDA needs these data on sales and marketing of specific products by sub-populations to determine whether the marketing of a particular product will have a beneficial health impact on the populations that are disproportionately impacted by tobacco.

⁸⁵ Lipari, RN & Van Horn, SL, “Smoking and mental illness among adults in the United States,” *The CBHSQ Report*: March 30, 2017. Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, Rockville, MD, https://www.samhsa.gov/data/sites/default/files/report_2738/ShortReport-2738.html.

⁸⁶ CDC, “Tobacco Product Use and Cessation Indicators Among Adults—United States, 2018,” *MMWR* 68(45):1013-1019, November 15, 2019, https://www.cdc.gov/mmwr/volumes/68/wr/mm6845a2.htm?s_cid=mm6845a2_w.

⁸⁷ RJ Reynolds. Project SCUM. Legacy Tobacco Documents Library. December 12, 1995. Access Date: August 27, 2013. Bates No.: 518021121/1129. URL: <http://legacy.library.ucsf.edu/tid/mum76d00>; Apollonio DE, Malone RE. Marketing to the marginalised: tobacco industry targeting of the homeless and mentally ill. *Tob Control*. 2005;14(6):409-15; RJ Reynolds. Our Target is (More) Downscale. 20 Sep 1989. RJ Reynolds. Bates No. 51 5603998/4000, <http://legacy.library.ucsf.edu/tid/pbs92d00>. Accessed August 23, 2013; RJ Reynolds. Project SCUM. Legacy Tobacco Documents Library. December 12, 1995. Access Date: August 27, 2013. Bates No.: 518021121/1129. URL: <http://legacy.library.ucsf.edu/tid/mum76d00>.

E. Use of Foreign Data

The proposed rule appropriately requires that when data from foreign countries in health risk investigations concern a demographic that is different from the United States, applicants should be required to provide “a scientific rationale for why the results of the study can be generalized to other demographic groups that are representative of the U.S. population as a whole.” 84 Fed. Reg. at 50600. FDA should apply this requirement rigorously, a standard that was not met by FDA’s unwarranted reliance of foreign data in its decision to grant PMI’s and Altria’s application for IQOS. There are numerous cultural, regulatory, and economic distinctions among U.S. and foreign populations that make reliance on foreign data problematic, particularly with respect to conclusions regarding consumer perception and market behavior.

TPSAC considered the use of foreign data when it met to review Swedish Match’s original MRTP application in April 2015. TPSAC voted 6 votes “no,” one vote “yes,” and one abstention on this question: “Does the Committee believe that the epidemiological data from Sweden concerning tobacco use behavior provide relevant information on the likelihood that current tobacco users in the U.S. will switch to the use of these snus products?” TPSAC also cast 5 votes “no,” with 3 abstentions, on the question: “Does the Committee believe that the epidemiological data from Sweden concerning tobacco use behavior provide relevant information on the likelihood that non-users of tobacco in the U.S. will initiate the use of these snus products?” TPSAC members stated the differences in sociocultural environment, marketing environment, and population demographics between Sweden and the U.S. as their reasons for voting “no.”⁸⁸

In order to evaluate the relevance of the behavior of individuals in different countries, it is necessary to take into account differences in culture, prior history, prior experience, laws and rules. There is no scientific basis for simply concluding that, because the population in one country responded to a product, or to how a particular product was marketed, in a particular way, that the population of another country will respond similarly. In light of the limitations noted by TPSAC and FDA on the use of Swedish data to predict the likely usage of snus modified risk products in the U.S., FDA’s decision, in its recent PMTA order on IQOS, to rely exclusively on data from Japan and Italy in concluding that “the current evidence indicates low IQOS uptake by youth” and assuming the same would occur in the U.S.⁸⁹ is, by any reasonable standard, arbitrary and impossible to defend from a scientific standpoint. In its MRTP decision on Swedish Match’s

⁸⁸ FDA, Meeting of the Tobacco Products Scientific Advisory Committee, April 9-10, 2015, Summary Minutes, June 15, 2015, <https://wayback.archive-it.org/7993/20170405201614/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM452547.pdf>. FDA, Meeting of the Tobacco Products Scientific Advisory Committee, Transcript from April 10, 2015, at 484-489.

⁸⁹ FDA, Technical Project Lead Review for PMI heated tobacco products, April 29, 2019, <https://www.fda.gov/media/131923/download>, at 83.

General Snus products, FDA noted, “FDA’s review of this evidence [from Sweden and Norway] concluded that it had limited applicability to the potential impacts of marketing the MRTPs in the U.S. FDA pointed to the range of social and cultural differences between the two marketing contexts—including that snus is a traditional Swedish product—limiting the validity of extrapolating from one to the other.”⁹⁰ However, in its Decision Summary for PMI’s IQOS PMTA, FDA appeared to have made a leap that the experiences among youth from Japan and Italy would occur in the U.S., without acknowledging nor identifying any “social or cultural differences” that could affect the translatability of the data from Japan or Italy to the U.S. context.⁹¹

FDA must require applicants to explain the use of foreign data and how those data are relevant to the U.S., given the specific differences in culture, policy, regulation, demographics, use patterns, and marketing between the two countries. In addition, whenever FDA itself relies on data from foreign countries in its evaluation of health risk investigations, FDA should be required to provide its own statement providing the rationale for such reliance and, where relevant, reasons why FDA concluded that it was not necessary to require the applicant to provide data from U.S. studies.

V. PROBLEMS CREATED BY CONFIDENTIALITY PROVISIONS

A. The application process does not permit adequate participation by stakeholders other than the applicant.

The purpose of the PMTA process is to enable FDA to make decisions about PMTAs that will best protect the public health. In order to accomplish this objective, FDA needs to consider the broadest possible range of information. A process that is designed to permit information inputs only from applicants will fail to provide FDA with that broad range of information. Stakeholders other than manufacturers have developed a large amount of the relevant information about ENDS products that will be the subject of the applications. An application process that does not permit them to participate will inevitably be based on incomplete information. This outcome is apparent in several different contexts.

B. Making even the identity of products for which PMTA applications have been filed confidential denies important information to consumers, other manufacturers, retailers, the public, and FDA enforcement personnel.

The provisions of the proposed rule regarding confidentiality fail to protect the public health and virtually guarantee that the only information FDA will get about a product will be that provided by the applicant itself unless FDA chooses to refer the application to the TPSAC. The

⁹⁰ FDA, Scientific Review of Modified Risk Tobacco Product Application (MRTPA) Under Section 911 (d) of the FD&C Act – Technical Project Lead, October 22, 2019, <https://www.fda.gov/media/131923/download>, at 39.

⁹¹ FDA, Technical Project Lead Review for PMI heated tobacco products, April 29, 2019, <https://www.fda.gov/media/131923/download>, at 83.

proposed rule would treat even the existence of a PMTA application as confidential. In justification of this policy, FDA alleges that a manufacturer's decision to consider the marketing of a new product may constitute a trade secret or confidential commercial information under FOIA exemption 4. However, the vast majority of products that will be the subject of these applications have actually been on the market for years and will remain on the market for one year or longer while the application is being reviewed. Whatever justification there might be for treating the existence of a PMTA application as confidential where the product is not yet on the market, there is no justification for confidential treatment for a product already available to consumers.

Under the Remedial Order of the United States District Court for the District of Maryland, the manufacturer of a new tobacco product would have to file an application by May 12, 2020 in order to keep the product on the market subsequent to that date. The confidentiality policy contained in the proposed rule would prevent consumers and other members of the public from knowing whether the manufacturer of a product they might be buying has filed an application. In other words, members of the public would have no way of establishing whether or not the product was on the market legally. The same consideration holds true for retailers. Legitimate retailers who want to only sell compliant products would have no reliable source to inform them whether the products they are selling have actually met the deadline for submitting an application and therefore can continue to be sold pending FDA action on the application. Moreover, in the absence of disclosure, manufacturers of competing products who have complied with their legal obligations will have no way of identifying products that are not legally on the market (since no such product can legally be sold in the absence of the filing of an application). Nor would FDA's own inspectors be able to enforce legal requirements without knowing what products were the subjects of PMTA applications.

FDA should amend the proposed rule to make public a list of products already on the market for which PMTA applications have been submitted. The public health importance of opening the PMTA process to the public outweighs the value of non-disclosure of the existence of an application even where the product is not yet on the market. Where the product is already on the market and can only remain on the market due to the filing of an application, there can be no valid argument against disclosure.

C. According confidentiality to the name of the manufacturer and the name of the product for which an application is filed is contrary to established FDA practice.

The policy stated in the proposed rule to accord confidentiality to the identity of a product that is the subject of a PMTA and the identity of the applicant is contrary to the Freedom of Information Act and contrary to established FDA practice that recognizes that this information is not confidential. In April 2016, Mark Greenwold, representing the Campaign for Tobacco-Free Kids, filed a Freedom of Information Act request seeking documents showing the name of each product that is the subject of a provisional substantial equivalence application that had not been granted, denied, or withdrawn and the name of the manufacturer of each such product.

(FOIA Request No. 2016-2087). On September 30, 2019, FDA released 3,915 pages of documents, of which 3,388 were released in full, showing the product and manufacturer names for more than 1,800 products subject to pending substantial equivalence applications. Although portions of some pages were redacted to avoid disclosure of certain information, FDA determined that neither the identity of products for which provisional substantial equivalence applications were pending nor the identity of the applicant was confidential and FDA disclosed this information. There is no principled reason why the identity of products already on the market (and their manufacturers) for which PMTAs have been submitted is any more confidential than that of products that are the subject of provisional substantial equivalence applications. FDA should amend the proposed regulation to provide for public disclosure of the names of such products and manufacturers.

D. The closed nature of the application process is likely to deny FDA important information about youth usage.

The problem FDA faces in obtaining full and accurate information about youth usage is greatly exacerbated by the closed nature of the application process that makes it impossible for the public to participate meaningfully. The large majority of studies regarding youth usage have been done by researchers outside the industry. While manufacturers are required to provide FDA with all investigations of which they are aware or reasonably should be aware, it is highly likely that a large amount of relevant information will come from research of which manufacturers are not aware. Much of the most relevant information may be from very recent research that has not yet been published. It is essential that FDA have access to this information in the evaluation of PMTA applications. In the absence of a process that enables the public to participate, FDA will never have before it the full scope of relevant evidence on youth usage and will not be able to fulfill its statutory obligation. FDA cannot adequately perform its statutory function if it conducts the application process solely as a dialogue between the applicant and the agency. There is a strong public interest in ensuring that the decisions FDA makes do in fact protect the public health and the only way to achieve this objective is to open the process to public participation.

As FDA notes, applications that are referred to TPSAC do become public (subject to redaction) and at least some form of public participation thereby becomes possible. The undersigned encourage FDA to refer to TPSAC all applications that raise significant questions of policy, both to enable FDA to obtain views from scientific experts outside the agency, but also to facilitate public participation.

E. Excluding stakeholders other than the applicant from the application process will prevent FDA from having adequate information about youth risk perception.

Development of probative information about youth perception of tobacco products is more likely to come from investigations done by stakeholders other than tobacco product manufacturers, particularly if FDA does not amend the proposed rule to make such direct investigations mandatory (see section IV.A.2, *supra*). Although FDA will presumably be aware

of published studies by such stakeholders, the use of an application process that does not permit direct participation of outside stakeholders may deprive FDA of important risk perception data and insights. Moreover, even though the applicant is required to produce all investigations including investigations with adverse results, it is not realistic to expect the presentation of evidence to FDA to be evenhanded. Even applicants that present both favorable and adverse information will seek to present all evidence in the light most favorable to their applications. Such a process inhibits FDA's ability to fulfill its statutory obligation to protect the public health because extensive research on ENDS products is ongoing and important findings may not have been published by the time FDA is considering the application. Unless wider participation in the process of consideration of PMTA applications is permitted, such findings would not be available to FDA.

VI. FDA'S PROCESS OF DECISION

A. Communications between FDA and Applicants

The proposed rule (sec. 1114.25) sets forth reasonable procedures for communications between FDA and applicants.

B. Provisions for Communications between FDA and Other Stakeholders

As a result of the closed and confidential nature of the premarket review process, nowhere in the proposed rule is any provision for communication between FDA and stakeholders other than the applicant in the consideration of premarket applications. The absence of such provisions reflects the erroneous view that the applicant is the only non-governmental party with an interest in the outcome of the application process and the equally erroneous view that the applicant is the only non-governmental party with the capability of making significant substantive contributions to the process of decision. As noted above, no matter how carefully the proposed rule prescribes an applicant's obligation to provide information, the application will be structured, to the maximum allowable extent, to serve the interest of the applicant. Parties other than the applicant and FDA may well have important information relating to the application that may not be available to the applicant or to FDA that would bear on FDA's ultimate decision. Therefore, in addition to making PMTAs and related materials available to the public, FDA should establish a mechanism for meaningful public input.

C. Acceptance Review

The proposed rule sets forth a procedure for an acceptance review during which FDA will determine if an application meets certain threshold requirements to qualify for further review. FDA explains that this procedure is designed to enable FDA to focus its resources on those submissions that are more likely to be filed for substantive review. The undersigned organizations support the establishment of such a procedure and urge FDA to retain it in the final rule.

D. Filing Review

The proposed rule sets forth a procedure for a filing review of applications that pass the acceptance review. FDA describes the purpose of the filing review as determining, prior to conducting a substantive review, whether a PMTA contains sufficient technical information to justify FDA's "commit[ment] of the considerable resources necessary to conduct substantive review of a PMTA." 84 Fed. Reg. at 50615. Section 1114.27(b)(1)(ii) requires a PMTA to contain "substantive information regarding certain categories of investigations described in section 1114.7(k)(1)" that is sufficient to meet the information threshold requirement in paragraph (ii). FDA properly notes that it expects manufacturers seeking to market a new product to have reviewed and included in their applications, inter alia, all the information from studies available on the FDA database, <https://www.fda.gov/tobacco-products/research/ctp-supported-tobacco-regulatory-research-projects>.

The undersigned organizations urge FDA to apply a standard of review that will enable it to distinguish between applications that contain scientific information arguably sufficient to address all the many issues relevant in determining whether the marketing of a product is APPH and those applications that do not. As FDA properly notes, this review will enable it to avoid the significant expenditure of resources it would otherwise commit to applications that clearly lack sufficient information to receive a marketing order.

FDA provides examples of information required to meet the requirements of the filing review. For ENDS products, these include the health risks of the new tobacco product compared not only to products in other categories but also the health risks of the product compared to other products in its category. As noted above in section III.A.4, it is not sufficient for an applicant to demonstrate that the health risks it raises are lower than the risks of cigarettes, but also that its marketing is APPH in light of the health risks it raises in comparison with other products in its category. For example, if an applicant urges that a product will produce a health benefit by enabling cigarette smokers to switch completely to that product, the application must also show that in doing so it does not raise a greater potential for tobacco use initiation by nonusers than other products in its category that may be capable of producing the same benefit. The proposed rule specifically requires the application to address abuse liability in the context of this filing review. 84 Fed. Reg. at 50616.

The proposed rule also properly requires the consideration in the filing review of "how consumers actually use the product, including use topography, product use frequency, use trends over time, and how such use affects the health risks of the product to individual users." 84 Fed. Reg. at 50616. Applicants that have had products on the market for several years should be expected to provide substantial information concerning these important considerations.

The proposed rule also requires information during the filing review on the potential impact of the product and its label, labeling and advertising on individuals' perceptions of the product and their use intentions. As FDA notes, "perceptions of the health risk of the product can influence decisions to use the product and. . .exposure to advertising can have a significant impact on the likelihood that nonusers of tobacco products, particularly youth, will initiate product use." 84 Fed. Reg. at 50616. This statement underscores the necessity for FDA to require in the final rule provision of all information regarding the advertising, promotion and marketing of the product from the date of the first advertisement until the date of the application (see section II.A, *supra*). An application that does not provide all such information should not advance beyond the filing review.

E. Substantive Review

FDA properly proposes to conduct "substantive review" only of applications that have met the requirements for filing review. Rigorous application of these requirements will enable FDA to concentrate its resources on applications for products that may actually have a potential to benefit the public health. However, as FDA notes, an application may meet the acceptance and filing requirements but still lack vital information that FDA needs to determine whether it should issue a marketing order. 84 Fed. Reg. at 50616, 50620.

FDA proposes to complete its review within 180 days after receipt of an application "except as described in §§1114.9 and 1114.27 (c)(4) & (5)." 84 Fed. Reg. at 50616. However, FDA proposes to begin the 180-day count on the day it receives the last piece of information necessary to complete the submission (including provision of product samples) and has numerous provisions for pausing the 180-day count when FDA requests provision of additional information from the applicant. It therefore appears likely that in many cases the actual interval between FDA's receipt of the application and its ultimate decision will be considerably more than 180 days.

The time necessary for FDA review is extremely important. FDA will be conducting PMTA review subject to the requirements of the order of the United States District Court for the District of Maryland in *American Academy of Pediatrics v. FDA*, 399 F. Supp. 3d 479 (D. Md. 2019). Pursuant to that order, applicants that file applications by May 12, 2020 will be able to keep their product on the market for one year from the date of application pending FDA decision on the application. If applications are not accepted for filing or if FDA issues a no marketing order within one year of the receipt of the application, the product may not remain on the market and becomes subject to an enforcement action. Moreover, under the terms of the order, a product that is the subject of an application that is still pending before FDA one year after the date of receipt may not remain on the market after that date and becomes subject to an enforcement action unless FDA exempts them from this requirement "for good cause on a case-by-case basis." *Id.*

The provisions of the proposed rule regarding the timing of FDA review make it likely that some applications will still be pending on May 12, 2021 and that in the absence of an exemption issued by FDA the product would become subject to an enforcement action even though the application was still pending. FDA has indicated that it intends to issue such exemptions only in situations where an application is close to resolution, where the applicant has done all it can to provide information to FDA on a timely basis, and it is likely that the application will be granted within a reasonable period of time. The undersigned organizations urge FDA to include in the final rule provisions making clear that such exemptions will be granted only on these conditions and not on a wholesale basis. FDA should also make it clear that of the six potential actions it may take after receiving an application for a tobacco product, Sec. 1114.29, all but the issuance of a marketing order under section 1114.31 have the effect of subjecting the tobacco product to an enforcement action.

F. Supplemental applications

The proposed rule contains provisions for the submission of a “supplemental application” for modifications to a product that has already received a marketing order pursuant to section 910. Sec. 1114.15; 84 Fed. Reg. at 50653. The proposed rule requires the submission of “sufficient information for FDA to determine whether any of the grounds for denial of an application pursuant to section 910(2) of the Federal Food, Drug and Cosmetic Act apply and a statement as to whether the new tobacco product would replace or extend the product line of the original product.” Sec. 115.15(d)(2). FDA should carefully review any applications submitted pursuant to this pathway to ensure that any products that are the subject of such an application receive as thorough a review as the original application and that the supplemental application process does not become a vehicle for products to reach the market without having undergone appropriate legal and scientific scrutiny.

VII. CRITERIA FOR GRANTING OR DENYING AN APPLICATION

As noted above, the statute establishes the criteria for the grant or denial of a PMTA application and designates the factors FDA is to consider. The statute directs FDA to deny an 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.” 21 U.S.C. 387j. Thus, as the proposed rule makes clear, the obligation to make this showing is on the applicant and thus the applicant bears the burden of establishing each of the elements of such a showing. 84 Fed. Reg. at 50618 (“an applicant cannot rely on FDA to seek out or create additional data to fill information gaps that may exist in a PMTA.”). The proposed rule is designed to inform potential applicants and the public what information an applicant needs to provide in order to meet this burden.

To meet this burden, an applicant must provide evidence sufficient to permit FDA “to identify and evaluate the risks and benefits the product presents to the population as a whole

including users and nonusers of the tobacco product” and to take into account of (A) the increased or decreased likelihood that existing users of tobacco products 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.” 21 U.S.C. 387j. In the proposed rule, FDA properly recognizes the complexity of this evaluation and the broad range of interests it encompasses. 84 Fed. Reg. at 50618 ([T]he APPH standard requires a balancing of product-specific potential risks and benefits. ...”).

It is likely that many applicants will claim that they lack information on the likelihood that nonusers of tobacco products, especially youth, will start using these products or that in the absence of clear evidence linking their particular product with youth initiation, FDA should grant their application. However, unless FDA concludes that the manufacturer has actually provided scientific evidence demonstrating that their product is *not* likely to increase initiation by nonusers, especially underage users, FDA must deny the application. Moreover, given the fact that the products that will be the subject of PMTAs filed in 2020 have been on the market for many years, manufacturers have had ample opportunity to develop scientific information about how their product is actually being used by specific populations.

The urgency of this matter is underscored by the scope of the epidemic of youth usage of ENDS products that has developed. Former FDA Commissioner Scott Gottlieb described the increase in youth e-cigarette usage between 2017 and 2018 as “the biggest one-year change in the history of the surveys that were done looking at youth usage of substances of addiction—the biggest change ever recorded in history year-over-year.”⁹² The 2019 figures from the National Youth Tobacco Survey showed another huge increase, that more than five million adolescents have become e-cigarette users, 27.5 percent of all high school students, an increase of 135 percent from 2017.⁹³ The severity of the epidemic has been recognized in numerous statements by FDA, by the Surgeon General, by the Secretary of HHS, and by the President.⁹⁴ Youth

⁹² “Scott Gottlieb on the CBD craze, vaping, and JUUL: A conversation with the former FDA commissioner,” AEI Banter Podcast, August 7, 2019, <https://ricochet.com/podcast/aei-banter/scott-gottlieb-on-the-cbd-craze-vaping-and-juul-a-conversation-with-the-former-fda-commissioner/>.

⁹³ Cullen, KA, et al., “e-Cigarette Use Among Youth in the United States, 2019,” *JAMA*, published online November 5, 2019. See also, Wang, T, et al., “Tobacco Product Use and Associated Factors Among Middle and High School Students — United States, 2019,” *MMWR* 68(12), December 6, 2019, <https://www.cdc.gov/mmwr/volumes/68/ss/pdfs/ss6812a1-H.pdf>.

⁹⁴ HHS, “Trump Administration Combating Epidemic of Youth E-Cigarette Use with Plan to Clear Market of Unauthorized, Non-Tobacco-Flavored E-Cigarette Products,” September 11, 2019, <https://www.hhs.gov/about/news/2019/09/11/trump-administration-combating-epidemic-youth-ecigarette-use-plan-clear-market.html>. U.S. Surgeon General, “Surgeon General releases advisory on E-cigarette epidemic among youth,” December 18, 2018, <https://www.hhs.gov/about/news/2018/12/18/surgeon-general-releases-advisory-e-cigarette-epidemic-among-youth.html>. HHS, “Secretary Azar Comments on Data Showing Rising E-Cigarette Use Among Youth,” November 15, 2018, <https://www.hhs.gov/about/news/2018/11/15/secretary-azar-comments-on-data-showing-rising-ecigarette-use-among-youth.html>. FDA, “Results from 2018 National Youth Tobacco Survey show dramatic increase in e-cigarette use among youth over past year,” November 15, 2018, <https://www.fda.gov/news-events/press-announcements/results-2018-national-youth-tobacco-survey-show-dramatic-increase-e-cigarette-use-among-youth-over>. FDA, “Statement from FDA Commissioner Scott Gottlieb, M.D., on

initiation of tobacco product use, in the form of ENDS products, is not merely a “likelihood;” it is an established fact and a matter of urgent concern.

In the face of this epidemic, claims by ENDS manufacturers, unsupported by evidence, that the epidemic is not attributable to their products, have no credibility. A manufacturer making such a claim should not have its application granted unless it demonstrates its truth through scientific evidence.

The statutory standard also requires FDA to consider other factors, including “the likelihood that current users of tobacco products will stop using them.” Applicants are likely to seek PMTAs based on anecdotal claims that a product has helped adult users quit using combusted tobacco products. FDA’s consideration of such claims should require that they be based on solid scientific data for their specific product. Given the fact that the products have been widely marketed for years prior to the filing of the applications, manufacturers should be required to submit such data. Moreover, manufacturers of new products currently on the market have had the opportunity to collect and should be required to provide data specific to the product for which the application is being made. Thus, even if it could be demonstrated that ENDS products as a broad category or some subcategory of ENDS products had contributed to current smokers switching completely to such products, a PMTA application should still be required to provide recent scientific data demonstrating that the specific product had enabled smokers to switch.

Furthermore, as the proposed rule makes clear, current users of ENDS products fall into several categories, including those who also continue to use combusted tobacco products as well as e-cigarettes and those who would have quit using tobacco products entirely but instead are using ENDS products. In calculating any potential benefit from the marketing of ENDS products, FDA should bear in mind that current tobacco users achieve a health benefit only if they switch completely to ENDS, i.e., if they quit the use of combusted tobacco products entirely. Dual or poly-tobacco use does not confer a health benefit⁹⁵ and a PMTA application claiming a public health benefit from helping current tobacco users reduce their use should take this into account. In addition, there is no health benefit to a smoker who switches to an ENDS

proposed new steps to protect youth by preventing access to flavored tobacco products and banning menthol in cigarettes,” November 15, 2018, <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-proposed-new-steps-protect-youth-preventing-access>. FDA, “Statement from FDA Commissioner Scott Gottlieb, M.D., on new steps to address epidemic of youth e-cigarette use,” September 11, 2018, <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-steps-address-epidemic-youth-e-cigarette-use>.

⁹⁵ CDC, “Dual Use of Tobacco Products,” March 22, 2018, <https://www.cdc.gov/tobacco/campaign/tips/diseases/dual-tobacco-use.html>. See also, Meier, E, et al., “A Randomized Clinical Trial of Snus Examining the Effect of Complete Versus Partial Cigarette Substitution on Smoking-Related Behaviors, and Biomarkers of Exposure,” *Nicotine & Tobacco Research*, Advanced Access, April 11, 2019. Wetter, D, et al., “Concomitant Use of Cigarettes and Smokeless Tobacco: Prevalence, Correlates, and Predictors of Tobacco Cessation,” *Preventive Medicine* 34:638-648, 2002. Hernandez, SL, et al., “Relationships Among Chewing Tobacco, Cigarette Smoking, and Chronic Health Conditions in Males 18–44 Years of Age,” *Journal of Primary Prevention* 38(5):505-514, 2017.

product, but would have otherwise stopped using tobacco products entirely in the absence of the ENDS product.

In addition, the public health calculus should take into account the different profiles of different ENDS products and the potential differences in their effects on various populations. The proposed rule provides, as an example, that if an application for a product that presents “significantly less toxicological risk to individual health than cigarettes in a marketplace where many addicted users currently smoke cigarettes” the applicant “could potentially receive an order where the PMTA demonstrates that the vast majority of individuals who would use the product would be current users of cigarettes who otherwise would not have quit and would switch to using the new product exclusively.” 84 Fed. Reg. at 50618. FDA states that for the same new product, the individuals who might use it are predominantly users of tobacco products with less toxicological risk, the application could potentially result in a no marketing order.” *Id.*

As the proposed rule recognizes, FDA’s evaluation of whether the marketing of an ENDS product is APPH depends not only on a comparison of the product to combusted tobacco products, but also on a comparison of the product to other products in the same category. For example, FDA may find that the marketing of an ENDS product is not APPH simply because there are other ENDS products that are equally effective at reducing the use of combusted tobacco products but less likely to cause nonusers to initiate.

VIII. POST-MARKET REVIEW

The provisions of the proposed rule for post-market review, §1114.41, appropriately require provision of information concerning products that are actually on the market. As noted above in these comments, all this information should be required with regard to products already on the market as part of the PMTA.

IX. OTHER ISSUES

A. Proposed Definitions for Terms Related to Product Sales

Among the definitions proposed for “commercially marketed,” “grandfathered tobacco product” and “test marketing” (84 Fed. Reg. at 50570-50571), it is unclear where products that have been offered as “limited editions” or “for a limited time” fit within these definitions. For instance, cigar manufacturers have introduced several “limited edition” flavors since August 8, 2016, which would appear to be in violation of the deeming rule.⁹⁶ FDA needs to provide clearer

⁹⁶ See, for instance, Swisher Sweets Limited Edition Sweet Cream, marketed as being introduced in January 2019, <https://www.cspdailynews.com/tobacco/swisher-introduces-sweet-cream>; White Owl White Russian Limited Edition, marketed as “available January 2019,” https://issuu.com/wtwhmedia/docs/csd_dec_2018/44; White Owl

guidance as to whether limited edition products are allowed, and if so, if they would be considered “test marketed” products or “commercially marketed.” Such information would be helpful for the public and retailers to understand what products should and should not be on the market. If FDA does not enforce against “limited edition” products, it would be a serious loophole for manufacturers to introduce new products without undergoing premarket review.

B. Proposed Data Requirements for RYO Tobacco and Pipe Tobacco

The proposed rule requests feedback on the specific “design parameters and information on performance criteria to be provided” for RYO tobacco (84 Fed. Reg. at 50588) and pipe tobacco (84 Fed. Reg. at 50593), but FDA questions if filler mass should be included for pipe tobacco. It is important that FDA keep the criteria and other submission requirements for these two products the same, since these products are difficult to distinguish from each other and manufacturers use the terms interchangeably. The Government Accountability Office (GAO) documented that manufacturers relabeled their RYO tobacco products as pipe tobacco to circumvent federal tax law,⁹⁷ and the U.S. Alcohol and Tobacco Tax and Trade Bureau (TTB) has yet to act on any of its requests for comments on proposed rules that would distinguish between the two products.⁹⁸

Even if these products are used differently and raise different questions of health risks, making the requirements for RYO tobacco and pipe tobacco mirror each other simplifies the review process by reducing the burden on FDA to spend time differentiating between the two products. It would also prevent manufacturers from circumventing any requirements that might apply to one product type but not another.

Respectfully submitted,

Action on Smoking & Health
Allergy & Asthma Network
American Academy of Family Physicians
American Academy of Oral and Maxillofacial Pathology
American Academy of Oral and Maxillofacial Radiology

Night Owl Cigars, marketed as “launching January 2019,” https://issuu.com/wtwhmedia/docs/csd_dec_2018/34;
Black & Mild Natural Wrap Cigar, marketed as being introduced “for a limited time” on its website in July 2018;
Swisher Sweets Limited Edition Passion Fruit, marketed as “to welcome...to the Limited Edition lineup” on July 18, 2019, <https://twitter.com/SwisherSweets/status/1151884758089117697>; Swisher Sweets Limited Edition Coco Blue, released in August 2018, “exclusively” at Circle K stores, <https://twitter.com/SwisherSweets/status/1025894282803273730>.

⁹⁷ U.S. Government Accountability Office (GAO), *ILLICIT TOBACCO: Various Schemes Are Used to Evade Taxes and Fees*, GAO 11-313, March 2011, <https://www.gao.gov/new.items/d11313.pdf>, at 13, 17.

⁹⁸ 75 Fed. Reg. 42659, 76 Fed. Reg. 52913, 77 Fed. Reg. 37287.

American Academy of Pediatrics
American Association for Dental Research
American Association for Respiratory Care
American Cancer Society Cancer Action Network
American College Health Association
American College of Cardiology
American College of Physicians
American Heart Association
American Society of Addiction Medicine
Association of Schools and Programs of Public Health
Asthma and Allergy Foundation of America
Big Cities Health Coalition
Campaign for Tobacco-Free Kids
ClearWay Minnesota
Common Sense Media
Counter Tools
Eta Sigma Gamma – National Health Education Honorary
National Association of County and City Health Officials
National Association of Pediatric Nurse Practitioners
National Association of School Nurses
National Association of Social Workers
National Network of Public Health Institutes
Oncology Nursing Society
Parents Against Vaping E-Cigarettes (PAVe)
Prevent Cancer Foundation
Public Health Law Center
Respiratory Health Association
Society for Cardiovascular Angiography and Interventions
Students Against Destructive Decisions
The Society of State Leaders of Health and Physical Education
Truth Initiative