1400 EYE STREET, N.W. • SUITE 1200 • WASHINGTON, DC 20005
PHONE (202) 296-5469 • FAX (202) 296-5427

February 7, 2020

Ms. Serine Hunter-Thomas
Office of Science
Center for Tobacco Products
U.S. Food and Drug Administration
Document Control Center, Bldg. 71, Rm. G335
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Re: Docket No. FDA–2019–N–0001, Tobacco Products Scientific Advisory Committee; Notice of Meeting re 22nd Century Group Inc.'s Modified Risk Applications for VLN™ King and VLN™ Menthol King

The Campaign for Tobacco-Free Kids (Tobacco-Free Kids) submits these comments in connection with the upcoming meeting of the Tobacco Products Scientific Advisory Committee (TPSAC) to consider the above-referenced modified risk tobacco product applications submitted by 22nd Century Group, Inc. (22nd Century) for two very-low-nicotine-content (VLNC) products: VLN™ King and VLN™ Menthol King. These are preliminary comments meant to inform the discussion before TPSAC, but because the formal comment period will not close until after the TPSAC meeting, and because the record that has been made available to the public is not complete, Tobacco-Free Kids reserves the right to submit more extensive comments on these applications prior to the close of the comment period.

In the subject applications, 22nd Century seeks to make modified exposure claims for two brands of its VLNC cigarettes.[1] The claims are presented, as they will appear on the cigarette packs, on p. 14 of the application's Executive Summary. On the front of the pack will appear the words "95% LESS NICOTINE," with the phrase "Helps reduce your nicotine consumption." The front panel also will include the following disclaimer: "Nicotine is addictive. Less nicotine does NOT mean safer. All cigarettes can cause disease and death." The claim "95% LESS NICOTINE, with the phrase "Helps reduce your nicotine consumption" also will appear on the

1 A marketing order was issued for 22nd Century's very low nicotine cigarettes on November 22, 2019.

back of the pack. However, the back of the pack also will include these words: "VLN smells, burns, and tastes like a conventional cigarette, but greatly reduces your nicotine consumption."

The applicant indicates that it is "requesting only Exposure Modification Orders at this time since it believes that scientific evidence is not currently available to assess the long-term risk of the products without conducting long-term epidemiological studies."[2] The applicant "intends to make no reduced risk or cessation claims, direct or implied . . . at this time." The implications of the applicant's choice to make only modified exposure claims are important for TPSAC to consider and are discussed throughout these comments.

I. HE VLN™ APPLICATIONS AND A PRODUCT STANDARD MANDATING NICOTINE REDUCTION IN CIGARETTES

In supporting the VLN™ applications, 22nd Century discusses FDA's recent recognition of the historic public health benefits of a product standard that would require the nicotine in all cigarettes to be reduced to minimally or non-addictive levels and the science supporting such a standard.[3] A nicotine product standard of this kind would prevent young people who experiment with smoking from becoming addicted and save them from a lifetime of addiction, tobacco-caused disease and premature death. It also would reduce the level of nicotine dependence in adult smokers, making it easier for them to quit and dramatically reducing the number of adult smokers. Indeed, FDA has estimated that reducing nicotine levels in cigarettes to non-addictive levels would prevent more than 33 million youth and young adults from initiating regular smoking by the year 2100. FDA estimates that, within five years, such a policy would cause 13 million smokers to quit, including 5 million within just the first year of implementation. Ultimately, more than 8 million lives would be saved by the end of the century.[4] Because of the promise of such unprecedented public health benefits, the public health community has expressed strong support for such a product standard, as reflected in the comments signed by forty public health and medical organizations submitted in response to FDA's Advance Notice of Proposed Rulemaking on a Tobacco Product Standard for Nicotine Level of Combusted Cigarettes (ANPRM).[5] Public health groups also have called for such a standard to apply, not just to cigarettes, but to cigars and all combustible products as well.

The comment period on the ANPRM closed 18 months ago and further action toward a rule mandating a nicotine product standard is long overdue. But it should be understood that the pending 22nd Century modified risk application raises an entirely different set of issues than a proposed low nicotine product standard. The public health impact of introducing a brand of VLNC cigarette, with modified exposure claims, into a market in which highly-addictive cigarettes remain readily available and aggressively marketed, will bear no similarity to the

---

2 Applications Executive Summary, at 3.

3 Applications Executive Summary, at 3-6.

4 Apelberg, BJ, et al., "Potential Public Health Effects of Reducing Nicotine Levels in Cigarettes in the United States," *New England Journal of Medicine*, published online March 15, 2018. See also Tobacco Product Standard for Nicotine Level of Combusted Cigarettes; Advanced Notice of Proposed Rulemaking, 83 Fed. Reg. at 11818 (March 16, 2018).

5 See comments of public health and medical organizations in Docket No. FDA-2017-N-6189 (July 16, 2018).

public health impact of an FDA mandate that no cigarette may be marketed unless it is minimally or non-addictive. As discussed more fully in these comments, the 22nd Century application raises such issues as whether smokers will switch to VLNC cigarettes or rather use them in conjunction with normal nicotine content (NNC) products (dual use), or whether their effect will be to delay cessation among smokers who would otherwise quit, or cause initiation among youth who perceive them to be "safe," creating a risk of progression to higher nicotine cigarettes. These kinds of issues do not arise with respect to the public health effects of a reduced nicotine product standard which makes higher nicotine cigarettes no longer legally available.

Thus, FDA should accelerate its consideration of a nicotine product standard, while TPSAC and FDA address the issues raised by the 22nd Century application independently, recognizing that the public health benefits of an industry-wide and mandated standard making all cigarettes non-addictive in no way establish the benefits of the proposed modified exposure claim for the VLN™ cigarettes.

II. THE STATUTORY STANDARDS THAT SHOULD GOVERN TPSAC'S CONSIDERATION OF THE MODIFIED RISK APPLICATION FOR VLM CIGARETTES

The Family Smoking Prevention and Tobacco Control Act of 2009 (Tobacco Control Act or TCA) assigns TPSAC a unique and central role in FDA's assessment of modified risk applications. The involvement of TPSAC in evaluating modified risk products is mandatory under the TCA.[6] In providing its evaluation, it is essential that TPSAC have a full understanding of the strict statutory standards applicable to modified risk applications and particularly the modified exposure claims proposed for VLN™ cigarettes.[7]

The VLN™ applications are governed by the standards set out in Section 911 of the Food, Drug and Cosmetic Act, as amended by the Tobacco Control Act. Section 911 was enacted as a response to the tragic history of false and misleading tobacco industry claims that certain tobacco products were less dangerous than other products, persuading health-conscious consumers to switch to the "reduced risk" products instead of quitting altogether.

In enacting the Tobacco Control Act, Congress made specific findings about the potential harm to public health from modified risk claims that should guide FDA in its consideration of any modified risk product application. Congress found that "unless tobacco products that purport to reduce the risks to the public of tobacco use actually reduce such risks, those products can cause

---

6 *See* Section 911(f)(1) of the Food, Drug and Cosmetic Act, as amended by the Tobacco Control Act, provides that FDA "shall refer" to TPSAC "any application" for a modified risk order.

7 Tobacco-Free Kids has addressed TPSAC's role in evaluating modified risk tobacco applications in multiple comments filed with FDA in recent years and incorporates those comments by reference. *See* Comments of Tobacco-Free Kids in Docket No. FDA-2017-N-0001, April 6, 2017 TPSAC meeting re review of modified risk applications (March 22, 2017); Comments of Tobacco-Free Kids, et al., in Docket No. FDA-2014-N-0001, April 18, 2014 TPSAC meeting re modified risk tobacco products (April 2, 2014; Comments of Tobacco-Free Kids, et al., Docket No. FDA-2013-N-0001-0056 re evaluation of risk and benefits of proposed modified risk tobacco products to population as whole (August 1, 2013); Comments of Tobacco-Free Kids in Docket No. FDA-2013-N-0001, April 30, 2013 TPSAC meeting re process for TPSAC consideration of modified risk tobacco product applications (April 23, 2013).

substantial harm to the public health. . . ." Sec. 2(37). Congress also found that "the dangers of products sold or distributed as modified risk tobacco products that do not in fact reduce risk are so high that there is a compelling governmental interest in ensuring that statements about modified risk products are complete, accurate, and relate to the overall disease risk of the product." Sec. 2(40). Congress determined that it is "essential that manufacturers, prior to marketing such products, be required to demonstrate that such products will meet a series of rigorous criteria, and will benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products." Sec. 2(36).

Under Section 911(a) and (b) the Tobacco Control Act, a "modified risk tobacco product" is defined as a tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products. A product is "sold or distributed" for such a use if, in relevant part,

> (1) [its] label, labeling, or advertising, either implicitly or explicitly [represents] that
>
> > (i) the tobacco product presents a lower risk of tobacco-related disease or is less harmful than one or more other commercially marketed tobacco products;
> >
> > (ii) the tobacco product or its smoke contains a reduced level of a substance or presents a reduced exposure to a substance; or
> >
> > (iii) the tobacco product or its smoke does not contain or is free of a substance,
>
> or…
>
> (3) the tobacco product manufacturer has taken any action directed to consumers through the media or otherwise, other than by means of the label, labeling, or advertising…that would be reasonably expected to result in consumers believing that the tobacco product or its smoke may present a lower risk of disease or is less harmful than one or more commercially marketed tobacco products, or presents a reduced exposure to, or does not contain or its free of, a substance or substances.

Thus, a modified risk product is defined in terms of the manufacturer's claims of reduced risk or reduced exposure in marketing the product, as well as its actions that may suggest to consumers that a product reduces risk or exposure to hazardous substances.

The 22nd Century VLN™ application seeks authorization under the "special rule" for certain modified risk products under Section 911(g)(2), where the label, labeling and advertising "is limited to an explicit or implicit representation that such tobacco product or its smoke does not contain or is free of a substance or contains a reduced level of a substance, or presents a reduced exposure to a substance in tobacco smoke." The claim "95% less nicotine" is such a claim. Section 911 expressly distinguishes such claims of reduced levels of a substance or reduced exposure to a substance (hereinafter referred to as "reduced exposure" claims) from claims that the product "presents a lower risk of tobacco-related disease or is less harmful" than one or more other tobacco products. Products making such "reduced risk" claims are governed by the standards in Section 911(g)(1), which requires both a showing that "as it is actually used by consumers" will (1) "significantly reduce harm and the risk of tobacco-related disease" to

users, and (2) "benefit the health of the population as a whole" taking into account both users and non-users of tobacco products.

The statute makes it clear that a product is eligible for authorization to be marketed with reduced exposure claims only if the scientific evidence is insufficient to meet the standards for demonstrating reduced risk. Thus, an applicant for an exposure modification order under 911(g)(2) must demonstrate that "the scientific evidence is not available and, using the best available scientific methods, cannot be made available without conducting long-term epidemiological studies" sufficient to meet the standards for a risk modification order under 911(g)(1). Thus, by seeking only an exposure modification order, 22nd Century is asserting that there is an absence of scientific evidence demonstrating that the claimed reduction in nicotine exposure will yield a reduction in disease risk. However, Section 911(g)(2) also requires a showing that the scientific evidence that *is* available without conducting long-term epidemiological studies "demonstrates that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies." *See* Section 911(g)(2)(A)(iv). Thus, the statute requires an applicant for a reduced exposure order to show a likelihood that future studies will show that the product's reduction in the level of harmful constituents will result in a substantial reduction in disease and death in consumers of the product. Clearly, the statute does not permit FDA to authorize a reduced exposure claim absent the likelihood that the science ultimately will show that the product reduces disease and death in users.

Although a reduced exposure order under the 911(g)(2) "special rule" does not require a showing of reduced risk, the statute requires the applicant to present sufficient evidence to allow FDA to make "additional findings" not required for a reduced risk order.

First, the applicant must show that the magnitude of the exposure reduction is "substantial," that the substances being reduced are harmful and that the product "as actually used" in fact exposes consumers to "the specified reduced level of the . . . substances." Section 911(g)(2)(B)(i).

Second, the applicant must show that the product, "as actually used by consumers" will not expose them to higher levels of other harmful substances, compared to other similar tobacco products, unless the increases are "minimal" and the likely overall impact of the product is to substantially reduce overall disease and death among individual users. Section 911(g)(2)(B)(ii).

Third, and of particular relevance to the VLN™ application, the applicant must have done actual consumer perception studies showing that the reduced exposure claim will not mislead consumers into believing that the product has been shown to be less harmful or to present a lower risk of disease than another tobacco product. Section 911(g)(2)(B)(iii). Thus, since a reduced exposure order would not be issued unless the currently available science is insufficient to show reduced risk from the product, the applicant must demonstrate that the claim does not cause consumers to believe that use of the product actually reduces risk. As discussed more fully below, given widespread consumer misperceptions linking nicotine with risk for smoking-related disease, TPSAC and FDA should carefully assess whether the claim "95% less

nicotine" will mislead consumers into believing that the science is sufficient to demonstrate that the VLN™ products reduce the risk of disease.

These consumer perception studies are particularly important given the appearance on the packages of the statement "Helps reduce your nicotine consumption." First, there is a serious question as to whether this statement is actually a reduced exposure claim, given that it is not a statement about the level of a harmful constituent in the product, but rather a statement the truth of which likely will depend upon the behavior of the smoker and how the VLN™ product is actually used. Second, the appearance of the statement is likely to increase the likelihood that consumers will misinterpret the reduced exposure claim (95% LESS NICOTINE) as a claim about reduced risk. Finally, as discussed further below, in assessing consumer perceptions of relative risk, it also will be important to determine the effectiveness of the proposed disclaimer that "less nicotine does NOT mean safer."

Fourth, the applicant for a reduced exposure order must show that the order "is expected to benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products." Section 911(g)(2)(B)(iv). As discussed below, given the current epidemic of e-cigarette use by adolescents, the likely perception of reduced exposure messages for VLN™ cigarettes by adolescents who use no tobacco products, and by adolescents who may be users of e-cigarettes, should receive special attention by TPSAC and FDA.

III. CONSIDERATIONS RELATED TO TPSAC'S EVALUATION OF THE APPLICATION'S IMPACT ON THE INDIVIDUAL USER AND THE POPULATION AS A WHOLE

A. Evaluating Population-Level Risks of VLN Cigarettes

As noted above, in order to obtain a modified exposure marketing order, the applicant must demonstrate that the issuance of such an order would benefit the health of the population as a whole taking into account both users and non-users of tobacco products. Demonstrating such a population-wide benefit requires a prediction of the effect of the proposed claim on consumer behavior. Even assuming that an individual who smokes cigarettes switches to VLN™ cigarettes as a result of the modified exposure claim, such benefits could be offset by (1) individuals who have never used tobacco products initiating smoking as a result of the claims; (2) individuals who might otherwise have quit smoking switching to VLN™ cigarettes instead of using safer, FDA-approved cessation methods as a result of the claims; (3) individuals engaging in dual use as a result of the claims; and (4) individuals who have quit smoking re-initiating with VLN™ cigarettes as a result of the claims. Thus, it becomes necessary to predict the effect of such claims on each potential group.

It is important that the public and consumers receive accurate information about different tobacco products, but it is equally essential that evidence be provided that those messages will not be misunderstood or create unintended consequences. Considering data showing

misperceptions about the health effects of nicotine, there needs to be a balance between providing this information to encourage smokers to switch completely and portraying the information in such a way that non-users, particularly youth, understand that smoking VLN™ cigarettes still carries health risks. This entails not only pre-review of messages, but also post-market evaluations.

For all these reasons, a determination of the effect of 22nd Century's proposed claims must depend principally on studies of consumer perception and consumer behavior in the United States. In evaluating this application, several issues should be considered as they pertain to consumer perception and behavior.

1. Claims should be considered in light of the population they are designed to target. The population as to which a modified exposure claim should be addressed is existing users of cigarettes. The effectiveness with which such a claim is targeted to this population may affect the appropriateness of granting the application. Thus, *to truly benefit the population, the applicant must adequately show that the message and design of its marketing materials, as well as its dissemination plan, is targeted exclusively to current adult smokers and exposure to youth and non-tobacco users is limited.*

   In any event, consideration of any modified risk claim should take into account the population actually most likely to encounter the claim, as opposed to the population intended to encounter the claim. While 22nd Century references "adult tobacco consumers" in its marketing plan, its marketing plan includes many images that include models under age 35 depicting smoking in a glamorous fashion. The marketing plan strategies, particularly social media and point of sale, will likely expose consumers other than adult smokers to the modified exposure claim.

2. Any claim should include sufficient information to avoid misleading or confusing consumers. Research shows that many smokers and non-smokers incorrectly link nicotine and tobacco-related disease, raising the possibility that smokers will mistakenly perceive a modified exposure claim for nicotine as a reduced harm claim. Further, as a reduction in nicotine consumption will only accrue if users completely substitute VLN™ cigarettes for normal nicotine content (NNC) cigarettes, adequate testing must be done to ensure that any modified risk claim clearly and explicitly communicates this message in a way that is fully understood by the public.

3. Given the history of tobacco companies misleading the public with fraudulent claims of reduced risk, like "light" and "low-tar" cigarettes, and marketing to youth to increase product sales, the worst-case, and perhaps

more likely, scenario would be if youth and nonsmokers misunderstand the message and believe that VLN™ cigarettes are "safe" to start using.

B. Do 22nd Century's Proposed Reduced Exposure Claims Mislead Consumers?

1. Will Consumers Interpret the Modified Exposure Claims As Modified Risk Claims?

Very low nicotine content cigarettes are not harmless; in fact, cigarettes with lower nicotine levels remain harmful and deadly. While nicotine is the primary addictive agent in cigarettes and is not benign, the overwhelming health consequences of smoking come from the more than 7,000 chemicals and 69 cancer-causing agents produced from combusted cigarettes.[8]

Studies of adult smokers have shown that they perceive lower nicotine cigarettes to be less harmful than regular nicotine content cigarettes, incorrectly linking nicotine content with risk for smoking-related disease. For example, a 2015-2016 nationally representative survey found that nearly half (47.1%) of smokers thought that smoking very low nicotine content cigarettes would be less likely to cause cancer than smoking regular cigarettes. [9] 2015 data from the FDA's nationally representative Health Information National Trends Survey (HINTS) found that three-quarters of people either did not know the relationship between nicotine and cancer (24%) or incorrectly believe that nicotine causes cancer (49%). It also found that 30 percent of respondents thought that very low nicotine content cigarettes were less harmful than regular cigarettes.[10] In research trials, smokers assigned to use very low nicotine content cigarettes also perceive them to be less harmful.[11] An online experiment with over 1300 adults, testing perceptions about a claim ("Imagine if tobacco companies were required to remove 95% of the nicotine from cigarettes.") similar to that of the applicant, found that while participants understood what 95% lower nicotine meant in terms of nicotine content and addictiveness, this claim was associated with lower accuracy about perceived cancer risks.[12] Finally, research about

---

8 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/.

9 Byron, JM, et al., "Public misperception that very low nicotine cigarettes are less carcinogenic," *Tobacco Control*, published online January 23, 2018.

10 O'Brien, EK, et al., "U.S. adults' addiction and harm beliefs about nicotine and low nicotine cigarettes," *Preventive Medicine*, 96: 94-100, 2017.

11 Denlinger-Apte, RL, et al., "Low nicotine content descriptors reduce perceived health risks and positive cigarette ratings in participants using very low nicotine content cigarettes," *Nicotine & Tobacco Research,* published online January 18, 2017. Pacek, LR, et al., "Perceived nicotine content of reduced nicotine content cigarettes is a correlate of perceived health risks," *Tobacco Control*, published online July 22, 2017. 2017.

12 Byron, M.J. "Reducing Nicotine Without Misleading the Public: Descriptions of Cigarette Nicotine Level and Accuracy of Perceptions About Nicotine Content, Addictiveness, And Risk," *Nicotine & Tobacco Research*, S101-S107, 2019.

Quest cigarettes, a very low nicotine content cigarette previously on the market, has also shown that people perceive them to be less harmful than other cigarettes.[13]

Given the overwhelming research demonstrating widespread misperceptions about the health harms from nicotine, the applicant must demonstrate that the proposed reduced exposure claim does not lead consumers to believe that VLN™ cigarettes are safer cigarettes. Further, consumers must not be misled to believe that reducing their nicotine consumption lowers their risk for tobacco-related disease. To the contrary, the applicant's consumer perception studies show that their claims are in fact misleading consumers. For example, themes identified in their qualitative research included, "There were misperceptions voiced regarding the health effects of nicotine use, as many were unsure about its impact relative to the other compounds found in tobacco smoke."[14] The company's quantitative consumer perception study also showed that current smokers ranked the VLN™ pack with the proposed modified risk claims (identified as "Consumption – Test 2" in the study) as having lower risk of critical disease, mortality and general health issues than the VLN™ pack without claims and lower risk than a comparator Marlboro Gold pack. As the study notes, "The results also suggest that Current Smokers associate reduced consumption of nicotine with lower health risk."[15] These findings clearly contradict the study's conclusion that the modified exposure message does not mislead consumers. The applicant has not met the burden of proof for the statute's criteria that a modified exposure claim not mislead consumers into believing the product is less harmful.

2. Will the Applicant's Disclaimer Statement Correct Misperceptions About the Modified Exposure Claim?

The applicant implies that adding a disclosure statement ("Nicotine is addictive. Less nicotine does NOT mean safer. All cigarettes can cause disease and death") corrects any misperceptions about the reduced exposure claim. However, the quantitative consumer perception studies referenced above *did* include the disclosure statement and yet *still* showed that consumers perceive the VLN™ pack with the proposed claims to be lower risk. Further, in their concluding recommendations, the contractor who conducted the qualitative consumer perception study found that, "Many statements, particularly on the Back of Pack, are seen as being wordy and won't necessarily be read," and that, "Many respondents noted that including benefits and drawbacks on the same panel can create confusion with consumers."[16] This is consistent with

---

13 O'Brien, EK, et al., "U.S. adults' addiction and harm beliefs about nicotine and low nicotine cigarettes," *Preventive Medicine*, 96: 94-100, 2017. Mercincavage, M, et al., "Reduced nicotine content cigarette advertising: how false beliefs and subjective ratings affect smoking behavior," *Drug & Alcohol Dependence*, 173: 99-106, 2017.

14 M/A/R/C® Research, "Qualitative Study to Develop PARE / VLN™ Hypothetical Claims Among U.S. Adult Cigarette Smokers, Adult Former Cigarette Smokers and Adult Never Cigarette Users Phases 1, 2, 3, and 4," at 16. (*Qualitative Study)*

15 M/A/R/C® Research, "Qualitative Study to Evaluate VLN Hypothetical Product messages Among U.S. Adult Cigarette Smokers, Adult Former Cigarette Smokers and Adult Never Cigarette Users," at 123. (*Quantitative Study*).

16 Qualitative Study, at 69.

research on other disclaimers on tobacco products. For example, Natural American Spirit is required to have disclaimers on their product and advertising (e.g., "Organic tobacco does NOT mean a safer cigarette"; "No additives in our tobacco does NOT mean a safer cigarette."), and yet research shows these disclaimers have little to no impact—consumers continue to perceive Natural American Spirit cigarettes are less harmful than other cigarettes.[17] TPSAC must give careful consideration to whether the applicant's proposed disclaimer statement will be sufficient to correct misperceptions about their modified exposure claim.

3. Do Consumers Accurately Understand How VLN™ Cigarettes Can Reduce Nicotine Consumption?

It is critical for modified exposure claims to use plain language that is easy for consumers to understand. One of the applicant's modified exposure claims includes the statement, "Helps reduce your nicotine consumption." CDC's Plain Language Thesaurus for Health Communication offers plain language alternatives for the word "consume."[18] Concern about this terminology was echoed by participants in the applicant's qualitative consumer perception studies, although this claim was only included in one out of the four phases of qualitative consumer perception studies, so little information is available as to how the phrase is understood. However, themes identified by the researchers in regards to this specific claim included that consumption "sounds too fancy."[19]

The likelihood that consumers will be misled by the statement "Helps reduce your nicotine consumption" is high, given that the statement is only accurate if consumers use VLN™ cigarettes in place of NNC cigarettes, not in addition to NNC cigarettes. However, this qualifying information is found nowhere on the pack. The proposed claims do not communicate to consumers that they must completely switch and use VLN™ cigarettes exclusively. Therefore, consumers may incorrectly believe that they can reduce their nicotine consumption by 95% with only occasional use of VLN™ cigarettes. Confusion about how VLN™ cigarettes can reduce your nicotine consumption was identified in the applicant's consumer perception studies. For example, a theme identified in the qualitative study was that the claim "Doesn't explain the link between lower nicotine content and reduction in smoking."[20] This confusion even led some participants to question whether the product was intended to function as nicotine replacement

---

17 Byron, M.J., et al., "Adolescents' and adults' perceptions of 'natural', 'organic' and 'additive-free' cigarettes, and the required disclaimers," *Tobacco Control,* published Online December 1, 2015. Baig, S.A., et al., "'Organic,' 'Natural,' and 'Additive-Free' Cigarettes: Comparing the Effects of Advertising and Disclaimers on Perceptions of Harm," *Nicotine & Tobacco Research*, published online February 26, 2018.

18 Centers for Disease Control and Prevention (CDC) National Center for Health Marketing, *Plain Language Thesaurus for Health Communications*, 2007, https://www.orau.gov/hsc/HealthCommWorks/MessageMappingGuide/resources/CDC%20Plain%20Language%20Thesaurus%20for%20Health%20Communication.pdf.

19 Qualitative Study, at 62.

20 Qualitative Study, at 62.

therapy (NRT) or as a cigarette. TPSAC should consider whether the modified exposure claim is sufficient to communicate *how* VLN™ cigarettes may reduce nicotine consumption.

4. Does Changing the Product Name to "Moonlight" Change Consumer Perceptions?

Just prior to FDA's grant of a PMTA for VLN cigarettes, 22nd Century filed an amendment to its PMTA indicating a name change for the product from VLN to "Moonlight".[21] In FDA's Scientific Review of the company's PMTA, reviewers expressed concern that the product name change to Moonlight "may appear on other labeling or advertising in a manner that highlights the descriptor 'light,' and may potentially be marketed as such without an MRTP order in effect."[22] Section 911(b)(2)(A)(ii) of the Tobacco Control Act includes any tobacco products labeled or advertised as "light," "low," or "mild" within the definition of modified risk tobacco products requiring an FDA order before they can be marketed. It is therefore significant that the applicant conducted consumer perception studies only using the VLN™ King/VLN™ Menthol King names, and not the name Moonlight.

Given the potential impact of the amended product name on perceptions of risk and potential interaction with how consumers may interpret the proposed reduced exposure claims, it is imperative for the applicant to conduct consumer perception studies using product and marketing mock-ups that use the amended product name. In fact, in its scientific review of the company's PMTA, FDA reviewers noted that the consumer perception study conducted "**is not relevant** given the name change proposed" (emphasis added).[23]

TPSAC should evaluate whether FDA can adequately assess the population-wide public health impact of a proposed modified risk product where the applicant has performed no consumer protection studies of the product with the brand name that will actually appear on the package and in the advertising.

5. Does 22nd Century's Marketing Impact Consumer Perceptions?

The applicant only submitted consumer perception studies on the proposed claim as mocked up on a cigarette pack. How the company markets the product will inevitably impact if and how these claims are actually read by consumers and how they are interpreted. Consumer perception studies should be conducted both with the pack and proposed marketing materials. The sample marketing materials submitted display the modified exposure claim in significantly larger font than the disclosure statement, increasing the likelihood that the disclosure statement will be ignored and consumers will be misled.[24] Further, the marketing materials (VLN Marketing Outline

---

21 U.S. Food and Drug Administration (FDA), 22nd Century PMTA Scientific Review: Technical Project Lead (TPL) for PM0000491 and PM0000492, at 6.

22 U.S. Food and Drug Administration (FDA), 22nd Century PMTA Scientific Review: Technical Project Lead (TPL) for PM0000491 and PM0000492, at 65, https://www.fda.gov/media/133633/download. (*PMTA Scientific Review)*

23 PMTA Scientific Review, at 66.

24 Cite to application.

and VLN Image Library) submitted by the applicant include imagery with young models in situations that glamorize smoking, which could attract non-tobacco users, including youth.[25]

TPSAC should consider how the applicant's marketing materials will influence consumer perceptions about the modified exposure claims and whether the applicant's marketing increases the likelihood that consumers will be misled. TPSAC should evaluate whether an application that presents no evidence of the effect of modified exposure claims in its product marketing can meet the public health standard.

C. Importance of Determining How VLN™ Cigarettes Will Actually Be Used by Adult Smokers

In order to assess whether the proposed reduced exposure claims will be "appropriate to promote the public health," TPSAC and FDA must consider how those claims will impact how VLN cigarettes are actually used by consumers. The FDA's Scientific Review of the company's PMTA concluded that, "Overall, it is anticipated that uptake of VLN™ cigarettes without any claims would be low."[26] Without uptake among adult smokers, there can be no possible benefit to the public health. Thus, a critical question is the extent to which the proposed modified exposure claims increase interest in and switching to VLN™ cigarettes among current adult smokers. This must be weighed against the possibility that the claim only results in dual use of VLN™ and NNC cigarettes, delayed cessation among smokers who would otherwise have quit using alternative methods, or uptake among formers smokers. Finally, any net benefits to adults cannot come at the expense of uptake among youth, which will be addressed in the following section.

Unlike the circumstances surrounding a reduced nicotine product standard, NNC cigarettes will continue to be readily available and aggressively marketed and smokers are unlikely to completely substitute NNC cigarettes for VLN™ cigarettes because very low nicotine cigarettes show low subjective appeal and experimental studies, including those submitted by the applicant, demonstrate low compliance rates and high levels of substitution with NNC cigarettes. There is no strong evidence that VLN™ can increase smoking cessation outside the context of a nicotine reduction product standard. In fact, the Surgeon General's 2020 report on smoking cessation concluded that, "The evidence is suggestive but not sufficient to infer that very-low-nicotine-content cigarettes can reduce smoking and nicotine dependence and increase smoking cessation when full-nicotine cigarettes are readily available; the effects on cessation may be further strengthened in an environment in which conventional cigarettes and other combustible tobacco products are not readily available."[27] This conclusion is echoed by the FDA, as noted in its scientific review of the applicant's PMTA: "The low subjective appeal, along with increased

---

25 Cite to application.

26 PMTA Scientific Review, at 68

27 HHS, *Smoking Cessation. 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, 2020.

craving and withdrawal, may prevent current smokers from fully transitioning to VLN™ cigarettes."[28] It is also important to note that in experimental studies using very low nicotine content cigarettes, participants are generally instructed to exclusively smoke the experimental cigarettes and discouraged from using NNC cigarettes. Even with such instructions, payment for participation and a free supply of VLN™ cigarettes, compliance is low. Use of VLN™ would likely be even lower in a real-world setting as has been the case for other failed commercial launches of VLNC cigarettes, such as Philip Morris's "Next" cigarette.[29].

If the marketing of VLN™ cigarettes with modified exposure claims only leads to experimentation and not sustained use among adult smokers, or leads to dual use of the VLN™ cigarettes with NNC cigarettes rather than complete cessation, there is unlikely to be a substantial health benefit to the population. A substantial body of evidence supports the proposition that the significant health benefits to an individual from quitting smoking occur only if the individual completely quits smoking. Merely reducing the number of cigarettes smoked or engaging in dual use of cigarettes and other tobacco products does not substantially reduce the health risk, as several U.S. Surgeon General's Reports and other studies have indicated that the risk of cardiovascular disease and other smoking-related diseases depends largely on the length of time a person smokes, not the number of cigarettes smoked.[30] According to the CDC, "If you only cut down the number of cigarettes you smoke by adding another tobacco product…you still face serious health risks. Smokers must quit smoking completely to fully protect their health – even a few cigarettes a day are dangerous."[31]

TPSAC must also consider whether a reduced exposure claim would hinder or delay cessation efforts by attracting adult smokers who would otherwise quit, perhaps using safer, FDA-approved cessation methods. In this situation, the modified exposure claim would not provide a population health benefit. As noted in FDA's Scientific Review of the company's PMTA, "Using VLN™ King and VLN™ Menthol King cigarettes compared to quitting tobacco use or completely switching to NRT would increase harm, as toxicant exposures would be similar to exposure resulting from the use of NNC cigarettes."[32] The applicant's consumer

---

28 PMTA Scientific Review, at 68

29 Dunsby, J, et al., "A nicotine delivery device without the nicotine? Tobacco industry development of low nicotine cigarettes." *Tobacco Control*, 13(4): 362-269, 2004.

30 U.S. Department of Health and Human Services (HHS), *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease*, U.S. Centers for Disease Control and Prevention (CDC), Office of Smoking and Health (OSH), 2010, at 9. HHS, *Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General*, CDC, OSH, 2012, at 22, http://www.surgeongeneral.gov/library/reports/preventing-youth-tobacco-use/index.html. Schane, RE, Ling, PM, & Glantz, SA, "Health Effects of Light and Intermittent Smoking: A Review," *Circulation* 121(3):1518-1522, 2010. Tverdal, A & Bjartveit, K, "Health Consequences of Smoking 1-4 Cigarettes per Day," *Tobacco Control* 14(5), 2005. Hackshaw, A, et al., "Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports," *BMJ* 360:j5855, http://doi.org/10.1136/bmj.j5855, 2018.

31 CDC, "Powerful new Tips from Former Smokers" ads focus on living with vision loss and colorectal cancer," CDC Press Release, March 26, 2015, http://www.cdc.gov/media/releases/2015/p0326-tips.html. See also: CDC, "Dual Use of Tobacco Products," http://www.cdc.gov/tobacco/campaign/tips/diseases/dual-tobacco-use.html.

32 PMTA Scientific Review, at 7.

perception study raise concerns that the modified exposure claim may lead to misperceptions about the role of VLN™ cigarettes in smoking cessation. In one phase of their qualitative study, a theme noted was that, "Many expressed confusion as to PARE / VLN's intended category: is it a cigarette or is it nicotine replacement therapy?"[33] These findings raise serious concerns about the possibility that the company's proposed modified exposure claims will lead to misperceptions about the product. Finally, in the quantitative consumer perception study, exposure to the proposed MRTP claims among smokers with intention to quit was associated with reduced intentions to use NRT.[34] If the applicant's claims deter smokers with intent to quit from using FDA-approved cessation products, there is a net public health harm.

Finally, any grant of a modified exposure application must be accompanied by a requirement of post-market surveillance of the actual impact of the MRTP claim on consumers. FDA should first consider requiring post-market surveillance on the availability of VLN™ cigarettes without modified exposure claims for a period of time before issuance of an MRTP order. This will allow for an appropriate comparison (changes in consumer behavior with and without the modified exposure claims) if FDA decides to grant the MTRP order. Although post-market surveillance is critical, it should not be regarded as a substitute for carefully designed pre-market consumer research to minimize the risk that the introduction of a MRTP will harm rather than benefit public health.

D. How Likely Would Youth Exposed to Modified Risk Messages be to Initiate Cigarette Smoking or Transition from Other Tobacco Product Use to Smoking?

It is essential that TPSAC carefully consider the likely impact on youth initiation of VLN™ cigarettes if marketed with modified exposure messages, including a possible gateway effect to smoking normal nicotine cigarettes. This concern was echoed in FDA's Scientific Review of VLN™'s PMTA, which noted that, "The applicant also did not provide any evidence to address the likelihood that never users who take up VLN™ cigarettes will switch to other tobacco products that present higher levels of individual health risk."[35] While research shows limited abuse liability of very low nicotine content cigarettes among youth smokers in experimental settings, TPSAC should consider the possibility that nicotine-naïve youth who perceive VLN™ cigarettes to be safe may experiment with the product and then graduate toward NNC cigarettes and sustained smoking behavior.

Special consideration should be given to the impact of a modified exposure claim on VLN™ Menthol King cigarettes in particular, as FDA has already concluded that menthol cigarettes increase youth smoking initiation.[36] FDA echoed this concern in its scientific review of 22nd Century's PMTA, noting that, "As menthol in NNC cigarettes facilitates experimentation and progression to regular smoking, it is unknown to what degree smoking VLN™ Menthol

---

33 Qualitative Study, at 19.

34 Quantitative Study, at 113.

35 PMTA Scientific Review, at 59.

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

King cigarettes may influence progression to regular smoking compared to NNC menthol cigarettes in new and inexperienced users, particularly youth and young adults."[37] The applicant did not provide any research on how menthol could impact the likelihood of initiation among youth.

22nd Century's proposed reduced exposure claim must also be considered in the context of the current youth e-cigarette epidemic and the current public discourse surrounding youth nicotine addiction. Altogether, over 5.3 million middle and high school students used e-cigarettes in 2019 – an increase of over three million users in just two years.[38] The number of youth now using e-cigarettes is alarming and the evidence is growing that e-cigarettes increase the susceptibility to long term addiction. The data are clear that youth who are using e-cigarettes are not just experimenting, but are becoming addicted at levels that have not been seen among kids who use cigarettes in decades. Among those who had used e-cigarettes in the past 30 days, 34.2% of high schoolers and 18% of middle schoolers were frequent users of e-cigarettes, using e-cigarettes on at least 20 of the preceding 30 days.[39] These statistics are confirmed by the reports of parents and pediatricians across the country. The problem is so severe that FDA convened a public hearing to gather input on how to help youth addicted to the nicotine in e-cigarettes. TPSAC should consider the likelihood that youth seeking to end their addiction to e-cigarettes, the "95% Less Nicotine" and "Helps reduce your nicotine consumption" claims may be interpreted as vaping cessation claims. Given that there is already research that youth e-cigarette use increases risk for smoking initiation, it is imperative for TPSAC to consider the potential population impact if youth e-cigarette users misinterpret 22nd Century's proposed modified exposure claims.

These concerns are heightened by the likelihood that the applicant's marketing will attract youth. The proposed marketing plan, while sparsely outlined, is likely to expose non-smokers, including youth, to the company's product and modified exposure claims. Sample marketing materials include young models in social situations that glamorize smoking and are likely to appeal to a younger audience. TPSAC should consider the likelihood that non-smokers, including youth, will be exposed to the modified exposure claims due to the applicant's marketing strategies. Further, TPSAC should consider how the applicant's marketing materials will influence consumer perceptions about the modified exposure claims, particularly among non-smokers and youth, and whether the applicant's marketing increases the likelihood that consumers will be misled. TPSAC should evaluate whether an application that presents no

---

37 PMTA Scientific Review, at 8.

38 Wang, TW, 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.

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

evidence on the effect of modified exposure claims in its product marketing can meet the public health standard.

Because the consumer perception and consumer behavior studies submitted by 22nd Century as part of its application do not address the impact on youth, a complete assessment of the impact of the modified exposure statement cannot be made by TPSAC or FDA, based on the data in the pending application. These types of evaluations must be done before modified exposure products are authorized by FDA, not only in post-marketing surveys and evaluations. Both FDA's Guidance for the preparation of Modified Risk Tobacco Product Applications and Institute of Medicine's (IOM) 2012 report, *Scientific Standards for Studies on Modified Risk Tobacco* recommend or even require the inclusion of youth in consumer perceptions studies of promotional material to determine the effect of such modified risk claims on adolescent risk perception or interest in using the product.[40] Given that adolescence is a period of heightened vulnerability for the initiation of tobacco use, it is important to evaluate whether adolescents accurately understand the purported benefits of an MRTP. Of particular importance are adolescents' perceptions of the risks and benefits of using the product, and whether they intend to initiate tobacco use with the MRTP rather than a traditional tobacco product because they believe the former is a "safe" alternative."[41] 22nd Century's failure to provide any evidence of the effect of these messages on adolescent risk perception is an inexplicable omission, against FDA's express instructions. The need to consider the effects of promotional statements on youth is vitally important in light of the tobacco industry's documented history of marketing tobacco products in ways that attract adolescents and the role that youth initiation has played—and continues to play—in the recruitment of long-term adult smokers.[42]

FDA's guidance on MRTP applications and IOM's report describe how such research should be done. Recognizing that research among non-smokers, and non-smoking youth in particular, requires care, FDA offered applicants an opportunity to work with the agency to determine the best way to conduct studies involving youth. [43] IOM suggested that such research could be appropriately done under the supervision of an independent third party.[44]

TPSAC should evaluate whether an application that presents no evidence on the effect of

---

40 FDA Draft Guidance, Modified Risk Tobacco Applications, March 2012, at 20.

41 Institute of Medicine, *Scientific Standards for Studies on Modified Risk Tobacco Products*, December 2011, ("IOM report") at 165.

42 U.S. Department of Health and Human Services (HHS), *Preventing Tobacco 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, 2012, at 530-41, 603-27 and sources cited therein; *U.S. v. Philip Morris*, 449 F. Supp. 2d at 561-691.

43 FDA 2012 Draft Guidance, at 26. IOM report at 7, 14, 50.

44 IOM report at 57.

modified risk claims on youth initiation or perception of risk can possibly meet the public health standard.

Respectfully submitted,

Campaign for Tobacco-Free Kids