



American Heart Association.



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Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: Docket No. FDA-2019-N-0994, Modified Risk Tobacco Product Applications for VLNTM King and VLNTM Menthol King, Combusted, Filtered Cigarettes, Submitted by 22nd Century Group

The undersigned public health organizations submit these comments on the above-referenced modified risk tobacco product (MRTP) applications submitted by 22nd Century Group, Inc. (22nd Century) for two very-low-nicotine-content (VLNC) cigarette products: VLNTM King and VLNTM Menthol King.¹

Like the FDA, many of our organizations are currently working around the clock to combat the global coronavirus pandemic (COVID-19). It has never been more important to take every measure possible to ensure lung and overall health. According to the Centers for Disease Control and Prevention (CDC), people with serious underlying medical conditions like heart disease, diabetes, and lung disease are at higher risk of getting very sick and developing more serious complications from COVID-19 illness.² Given that there is conclusive evidence that cigarette smoking increases the risk for respiratory infections, weakens the immune system, and harms nearly every organ of the body, the coronavirus pandemic underscores the importance of careful FDA assessment of the population-wide impact of any proposed claim by a cigarette company that its products are less hazardous, or contain lesser amounts of particular substances, than other cigarettes.

For the reasons detailed below, we believe that any careful assessment of the 22nd Century applications should result in denial of those applications.

I. SUMMARY OF REASONS THE VLNTM APPLICATIONS SHOULD BE DENIED

The subject applications seek to make modified risk claims for two versions of 22nd Century's VLNC cigarettes.³ The three proposed MRTP claims that would be used in the products' labeling and advertising include: (1) "95% less nicotine," (2) "Helps reduce your

¹ 84 Fed. Reg. 35869 (July 25, 2019).

² CDC, Are You at Higher Risk for Severe Illness?, 2020, <https://www.cdc.gov/coronavirus/2019-ncov/specific-groups/high-risk-complications.html>.

³ A marketing order allowing introduction into interstate commerce was issued for 22nd Century's VLNC cigarettes under the product names Moonlight and Moonlight Menthol on December 17, 2019.

nicotine consumption,” and (3) “. . . greatly reduces your nicotine consumption.”⁴ An additional proposed disclaimer that would appear on the products’ labeling and some advertising would read: “Nicotine is addictive. Less nicotine does NOT mean safer. All cigarettes can cause disease and death.”⁵

The applicant is clear 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.”⁶ The applicant also states it “intends to make no reduced risk or cessation claims, direct or implied . . . at this time.”⁷ The implications of 22nd Century’s choice to make only reduced exposure claims are important as the Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Family Smoking Prevention and Tobacco Control Act of 2009 (Tobacco Control Act) provides a distinct set of criteria for issuing exposure modification orders.⁸

The burden is on the applicant to provide FDA sufficient evidence in its application to allow the agency to make each of the statutory findings required to issue a modified risk order. The FDA does not have sufficient information before it on a number of issues to grant exposure modification orders for the VLNTM products. The FDA should deny 22nd Century’s VLNTM MRTP applications for the following reasons:

- The current marketplace (continued availability of high nicotine cigarettes) does not permit FDA to find the VLNTM products, marketed with the proposed claims, will either achieve the public health benefits of a category-wide nicotine-reduction product standard or better enable the public to understand modified risk information relative to total health and in relation to all tobacco products.
- In light of the historical basis for the statutory MRTP provisions and the applicant’s actions, the proposed and likely MRTP claims for the subject products are not appropriately limited or supported by sufficient evidence to permit FDA to issue exposure modification orders.
 - There is insufficient evidence of (1) a reasonably likely substantial reduction in morbidity or mortality among individual tobacco users; (2) consumers in fact being exposed to 95% less nicotine as the product is actually used; (3) actual consumer perception studies of the MRTP claims demonstrating that consumers will not be misled; and (4) an expected benefit to the health of the population as a whole.

⁴ 22nd Century Briefing Document for TPSAC, at 3.

⁵ FDA Briefing Document for TPSAC, at 5-6.

⁶ Applications Executive Summary, at 2-3.

⁷ *Id.* at 2.

⁸ Section 911(g)(2)(A) and (B). *See also* FDA Draft Guidance, Modified Risk Tobacco Applications, March 2012, at 3-4.

- The subject products' name change to Moonlight in combination with the proposed claims, disclosure statement, and sample marketing materials raise serious concerns that consumers will be misled.
- There is an absence of any youth data and sufficiently convincing evidence to show that marketing of the subject products with the proposed claims will not lead to concerning patterns of tobacco use among important subpopulations, including youth and African Americans. As a result, FDA cannot make the statutorily-required findings necessary for it to issue the requested exposure modification orders.

II. THE VLN™ APPLICATIONS MUST BE ASSESSED IN THE CONTEXT OF THE CURRENT MARKETPLACE: ABSENT A NICOTINE-REDUCTION PRODUCT STANDARD AND AMIDST A NEVER-ENDING STREAM OF 'NEW' TOBACCO PRODCUTS

In supporting its VLN™ applications, 22nd Century discusses FDA's recognition of both 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.⁹ 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 reduce 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 2100.¹⁰ Additionally, within five years, such a policy would cause 13 million smokers to quit, including five million within just the first year of implementation, and ultimately, more than eight million lives would be saved by the end of the century.¹¹ Because of the promise of such unprecedented public health benefits, the public health community has expressed strong support for such a product standard. This is 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).¹² 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.¹³

⁹ Applications Executive Summary, at 3-6.

¹⁰ Tobacco Product Standard for Nicotine Level of Combusted Cigarettes; Advance Notice of Proposed Rulemaking, 83 Fed. Reg. 11818, 11837 (March 16, 2018) (citing 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).

¹¹ *Id.*

¹² Comment from Tobacco-Free Kids et al. in Docket No. FDA-2017-N-6189 (July 16, 2018).

¹³ *Id.* at 6-13.

The comment period on the ANPRM closed almost two years ago, and further action toward a rule mandating a nicotine product standard is long overdue. But as was made clear at the Tobacco Products Scientific Advisory Committee (TPSAC) meeting on the subject applications, it must be understood that the pending 22nd Century MRTP applications raise an entirely different set of issues than a proposed low nicotine product standard. The public health impact of introducing a brand of VLNC cigarettes, with reduced exposure claims, into a market in which highly-addictive cigarettes remain readily available and aggressively marketed, will bear no similarity to the public health impact of a category-wide FDA mandate that no cigarette may be marketed unless it is minimally or non-addictive. As discussed more fully later in these comments, the 22nd Century applications raise such issues as whether smokers will switch to VLNC cigarettes or rather dual use them in conjunction with normal nicotine content (NNC) cigarettes, 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 specific issues do not arise with respect to the public health effects of a reduced nicotine product standard because higher nicotine cigarettes would no longer legally be available.

In fact, absent a reduced-nicotine rule for all cigarettes, the subject applications bring to life the possible countervailing effects discussed in the ANPRM of continued combusted tobacco product use via product migration or transition to dual use with other combusted tobacco products.¹⁴ The FDA’s proposed solution to this particular concern in the ANPRM was to consider a *more* comprehensive product standard covering cigarettes *and* other combusted tobacco products, not a less comprehensive approach as would be the case with the subject products in the current marketplace. Thus, FDA should explicitly recognize that the public health benefits of an industry-wide and mandated standard making all cigarettes non-addictive in no way establishes the benefits of the proposed MRTP claims for 22nd Century’s VLNTM cigarettes.

The potential problems of dual- or poly-tobacco product use, delayed cessation, and new or re-initiation of tobacco use that VLNTM cigarettes pose in the existing environment are also exacerbated by the rapidly evolving tobacco marketplace. A plethora of products advertised as “new” continue to be introduced without either premarket review, including substantiation of health-related claims, or robust enforcement that matches the speed of change in a dynamic marketplace. While there are a number of forces at play, it is undeniable that misperceptions about relative risk run rampant. These misperceptions are not something 22nd Century should be allowed to take advantage of or dismiss as unfixable. The applicant bears the burden of showing not only that its proposed MRTP claims will not be adverse to public health, but that as actually used, the MRTPs are likely to enhance public health. The pending applications do not meet this burden. Thus, the FDA should swiftly deny the VLNTM applications and accelerate both its consideration of a nicotine product standard and strict enforcement of statutorily-required premarket review.

¹⁴ ANPRM, *supra* note 10, at 11820.

III. SUMMARY OF STATUTORY MODIFIED RISK STANDARDS AS APPLIED TO THE VLN™ APPLICATIONS

- A. The historical basis of Section 911 of the FD&C Act, as amended by the Tobacco Control Act, serves as a reminder of the need for FDA to rigorously apply the statutory standards.

The VLN™ applications are governed by the standards set out in Section 911, which was enacted in response to a massive evidentiary record of fraudulent health and “reduced risk” claims made by tobacco product manufacturers over the course of more than fifty years.¹⁵ Those claims caused millions of Americans to initiate cigarette smoking who otherwise would not have done so and caused millions of American smokers to continue smoking when they otherwise would have quit. In the absence of this massive industry fraud, literally millions of deaths, and untold suffering, would have been avoided.

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 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). And importantly for the subject applications, Congress unambiguously stated that “[p]ermitting manufacturers to make unsubstantiated statements concerning modified risk tobacco products, whether express or implied, even if accompanied by disclaimers would be detrimental to the public health.” Sec. 2(42).

A central component of the tragic history of false and misleading tobacco industry claims that certain tobacco products were less dangerous than other products was the “light” and “low-tar” fraud. Smokers were made to believe that cigarettes labeled and advertised with descriptors such as “light” were safer than other cigarettes, but the companies knew that, as actually used by smokers, such cigarettes were no less hazardous. Health-conscious consumers were persuaded to switch to supposed “reduced risk” products instead of quitting altogether. Two years ago, corrective statements telling the truth about “light” and “low tar” cigarettes were finally ordered to be visible on cigarette packages, product websites, and newspaper and television advertisements under a court order issued by the U.S. District Court for the District of Columbia in the federal government’s massive RICO case against cigarette companies.¹⁶ The Court found

¹⁵ *U.S. v. Philip Morris USA Inc.*, 449 F. Supp.2d 1 (D.D.C. 2006), *aff’d in relevant part*, 566 F.3d 1095 (D.C. Cir. 2009), *cert. denied*, 130 S.Ct. 3501 (2010).

¹⁶ *U.S. v. Philip Morris USA Inc.*, No. 99-CV-2496-GK, Dkt. No. 6260 (May 1, 2018).

these statements were necessary because the companies were likely to continue their fraudulent conduct in the future. Thus, in light of the history of false claims of “reduced risk” products by tobacco companies and the finding by a federal court that the industry is likely to continue its fraudulent conduct, FDA should ensure that the statutory standards, enacted by Congress to prevent a similar public health disaster from ever happening again, are rigorously applied to 22nd Century’s VLN™ applications.

B. The pending applications must meet the authorization criteria under the “special rule” for certain modified risk products.

An MRTP is defined in the Tobacco Control Act as “any 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.” Sec. 911(b)(1). A product is “sold or distributed” for such a use if:

- (i) [its] label, labeling, or advertising ... represents explicitly or implicitly 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;
- (ii) [its] label, labeling, or advertising ... uses the descriptors “light,” “mild,” or “low” or similar descriptors; or
- (iii) the tobacco product manufacturer [takes] 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.

Sec. 911(b)(2)(A). Thus, a modified risk product is defined in terms of the manufacturer’s claims of reduced risk or reduced exposure in marketing the product, its use of certain descriptors, and its actions that may suggest to consumers that a product reduces risk or exposure to hazardous substances.

The 22nd Century VLN™ applications seek authorization under the “special rule” for certain modified risk products 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.” Sec. 911(g)(2)(A)(ii). The applicant’s proposed claim “95% less nicotine” is such a representation, but as discussed further below, 22nd Century has failed to demonstrate that either of its other two proposed claims are sufficiently limited as required for FDA to issue exposure modification orders under Section 911(g)(2).

1) Product name change to Moonlight

The FDA's briefing document for TPSAC's consideration of the subject applications noted seven additional claims in the submitted proposed advertising.¹⁷ The agency also noted at the TPSAC meeting that while the subject products use the brand name VLN in the MRTP applications, the premarket tobacco product application (PMTA) orders were issued using the brand name Moonlight.¹⁸ While FDA did not specifically seek TPSAC input on either the additional claims or the name change, both represent early signals of 22nd Century's willingness to push the limits established by Section 911(g)(2). The name change in particular raises important questions about whether the subject products' MRTP claims will be accompanied by the brand name Moonlight, which contains within it the prohibited "light" descriptor, and for which the applicant did not produce any evidence. The applicant conducted consumer perception studies using only the VLNTM King and VLNTM Menthol King brand names, and not the brand name Moonlight. Multiple TPSAC members raised concerns about the name change during its deliberations on the subject applications.¹⁹

Additionally, in FDA's scientific review of the company's PMTA (PMTA Scientific Review), 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."²⁰ As previously described, Section 911(b)(2)(A)(ii) of the Tobacco Control Act includes any tobacco product labeled or advertised as "light" within the definition of an MRTP, which requires an FDA order before it can be marketed. These comments reiterate FDA's own concerns, as well as those of TPSAC, and conclude that because FDA cannot be certain that "the label, labeling, and advertising ... that would cause the [subject] tobacco product[s] to be [MRTPs will be] 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," as required by Section 911(g)(2)(A)(ii), the applications should be denied.

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 the PMTA Scientific Review, FDA reviewers noted that the consumer perception study conducted "*is not relevant*

¹⁷ FDA Briefing Document for TPSAC, at 10.

¹⁸ TPSAC Meeting Transcript, at 16.

¹⁹ *Id.* at 169 et seq. where Dr. Warner, Ms. Herndon, and Ms. Becenti expressed concern about the name change to Moonlight. Dr. Ogden raised a question about exact wording related to the product name, and Chair Mermelstein summarized Committee sentiment that the name VLN is less concerning than Moonlight.

²⁰ FDA, 22nd Century PMTA Scientific Review: Technical Project Lead (TPL) for PM0000491 and PM0000492, at 65.

given the name change proposed” (emphasis added).²¹ Thus, FDA must get clarity from 22nd Century as to whether the proposed modified risk claims will be used with a product called “Moonlight.” The FDA should not approve applications that include no consumer perception studies of the product with the brand name that will actually appear on the package and in product advertising.

2) “Reduced exposure” vs. “reduced risk” claims

Section 911 expressly distinguishes claims of reduced levels of a substance or reduced exposure to a substance (“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). 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.” 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, which 22nd Century did not do. 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 an exposure modification 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).

²¹ *Id.* at 66.

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™ applications, the applicant must have done actual consumer perception studies showing that the reduced exposure claims, as the applicant will label and market the products, 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). Since an exposure modification 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 diseases, FDA should conclude that the evidence is insufficient to ensure consumers will not be misled into believing that the VLN™ products reduce the risk of disease.

These consumer perception studies are especially important given the appearance of the statement, “Helps reduce your nicotine consumption,” on the front of packages and, “... greatly reduces your nicotine consumption,” on the back of packages.²² First, there is a serious question as to whether these statements are actually reduced exposure claims, 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 statements is likely to increase the chances that consumers will misinterpret the reduced exposure claim, “95% less nicotine” as a claim about reduced risk. Third, as discussed further below, in assessing consumer perceptions of relative risk, 22nd Century has not demonstrated the effectiveness of the proposed disclaimer about the harms of nicotine and cigarettes. For these reasons, FDA cannot be sure that the subject products’ MRTP advertising and labeling “enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation to all of the diseases and health-related conditions associated with the use of tobacco products” as required by Section 911(h)(1) to issue a modified risk order. Thus, the VLN™ applications should be denied.

Finally, the applicant for an exposure modification 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). Given the current epidemic of e-cigarette use by adolescents, FDA must pay special attention to the likely perception of reduced exposure claims for VLN™ cigarettes by not only adolescents who use no tobacco products, but by adolescents who may be users of e-cigarettes or other tobacco products as well. Manufacturers of modified risk products bear the burden of demonstrating that MRTP claims, as they will be used in labeling and advertising, will neither exacerbate the current concerning patterns of tobacco product use by youth nor create

²² Applications Executive Summary, at 10.

new ones. Tobacco companies also should not be allowed to take advantage of a rapidly evolving marketplace where a myriad of tobacco products and claims continue to be introduced and allowed without robust premarket review enforcement, creating confusion among users and nonusers alike about the relative risk profiles of both categories of products and specific products within a category. The FDA has the power to prevent this, and we urge the agency to forcefully exercise its authority, including denying the subject applications.

IV. THE VLN™ APPLICATIONS SHOULD BE DENIED BECAUSE THE REDUCED EXPOSURE CLAIMS MISLEAD CONSUMERS

- A. Consumers believe that nicotine causes tobacco-related disease and that reduced nicotine cigarettes are safer.

As highlighted by Dr. Byron's presentation at the TPSAC meeting, studies of adult smokers show 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.²³ For example, a 2015-2016 nationally representative survey found that nearly half (47.1%) of smokers thought that smoking VLNC cigarettes would be less likely to cause cancer than smoking regular cigarettes.²⁴ 2015 data from 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 believed that nicotine causes cancer (49%). It also found that 30 percent of respondents thought VLNC cigarettes were less harmful than regular cigarettes.²⁵ In research trials, smokers assigned to use VLNC cigarettes also perceive them to be less harmful.²⁶ An online experiment with over 1300 adults tested perceptions about a claim similar to that of the applicant²⁷ and found that while participants understood what 95% lower nicotine meant in terms of nicotine content and addictiveness, the reduced exposure claim was associated with lower accuracy about perceived

²³ Byron, MJ, *Investigating and Addressing the Perceived Risk of Nicotine and Very Low Nicotine Cigarettes*, Presentation to TPSAC, February 14, 2020.

²⁴ Byron, MJ, et al., "Public misperception that very low nicotine cigarettes are less carcinogenic," *Tobacco Control*, published online January 23, 2018.

²⁵ O'Brien, EK, et al., "U.S. adults' addiction and harm beliefs about nicotine and low nicotine cigarettes," *Preventive Medicine*, 96: 94-100, 2017.

²⁶ 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.

²⁷ The claim in the online experiment was, "Imagine if tobacco companies were required to remove 95% of the nicotine from cigarettes."

cancer risks.²⁸ Finally, research about Quest cigarettes, a VLNC cigarette previously on the market, has also shown that people perceive them to be less harmful than other cigarettes.²⁹

B. The applicant's consumer perception studies demonstrate that consumers mistakenly believe VLN™ cigarettes are safer.

The applicant's consumer perception studies confirm that their claims are in fact misleading consumers. For example, themes identified in their qualitative research (Qualitative Study) 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."³⁰ The company's quantitative consumer perception study (Quantitative 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."³¹ These findings clearly contradict the study's conclusion that the reduced exposure message does not mislead consumers.

Finally, during the TPSAC meeting, TPSAC members raised concerns about the qualitative consumer perception studies conducted by the applicant. Dr. Thrasher raised the question of whether the applicant conducted qualitative studies on the final messaging chosen to be tested in the quantitative studies, to which Dr. Carmines of Carmines Consulting, who presented on behalf of 22nd Century, responded, "We tested parts and pieces of it, that led us to, at the end, to the final quantitative. So, yes, we refined the labeling throughout this process to try to convey the message. But we did not run a qualitative study at the end on what we were running our quantitative study on."³² Qualitative studies are needed to provide a complete understanding of how potential users process and interpret the messaging.

Based on this evidence, the applicant has not met its statutory burden of demonstrating that its reduced exposure claims do not mislead consumers into believing the product is less harmful. As a result, FDA must deny the pending applications.

²⁸ Byron, MJ, "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.

²⁹ 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.

³⁰ 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.

³¹ M/A/R/C® Research, "Quantitative Study to Evaluate VLN Hypothetical Product Messages Among U.S. Adult Cigarette Smokers, Adult Former Cigarette Smokers and Adult Never Cigarette Users," at 123.

³² TPSAC Meeting Transcript, at 82-83.

- C. Disclaimer statements are not an effective health communication strategy. The applicant’s disclosure statement does not correct misperceptions about the health effects of VLN™ cigarettes.

The applicant claims 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, no evidence was presented to support this claim. The quantitative consumer perception studies referenced above *did* include the disclosure statement and yet *still* showed that consumers incorrectly perceived the VLN™ pack with the proposed claims to be lower risk. It is important to note that none of the conditions in the quantitative study allowed for the testing of the disclaimer statement specifically because it was included in all experimental conditions. While it is unknown if the claim mitigated or exacerbated misperceptions, it is clear the disclosure is insufficient to correct misperceptions. Further, in their concluding recommendations, the applicant’s contractor who conducted the Qualitative 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.”³³

Concerns about the effectiveness of the disclaimer statement are heightened by the fact that the applicant did not test the impact of it in the context of its marketing materials. As shown in Appendix 1, the font size of the disclaimer statement is significantly smaller than the other text in advertising materials, and in some cases, it is even obscured by the graphics. Further, in some marketing materials, no disclaimer statement is included. The applicant thus failed to conduct appropriate studies to assess perception and understanding of the disclaimer statement in a real world context, which includes the context in which the product is marketed.

Research on disclaimer statements consistently finds them to be ineffective.³⁴ As concluded by Dr. Byron in his presentation to TPSAC, disclaimer statements are neither “grounded in communication and persuasion science” nor supported by the science.³⁵ He summarized that disclaimers fail because they are not noticed by consumers, and are discounted, distrusted, and misinterpreted.³⁶ One specific example demonstrating this is related to the disclaimers required on and in Natural American Spirit’s product and advertising.³⁷ Despite the

³³ Qualitative Study, *supra* note 30, at 69.

³⁴ Green, KC, Armstrong, JS. (2012). Evidence on the effects of mandatory disclaimers in advertising. *J Public Policy Mark*, 31(2), 293-304; Kesselheim, AS, Connolly, J, Rogers, J, Avorn, J. (2015). Mandatory disclaimers on dietary supplements do not reliably communicate the intended issues. *Health Affairs*, 34(3), 438-446. doi:10.1377/hlthaff.2014.0515.

³⁵ TPSAC Meeting Transcript, at 220-21.

³⁶ Byron, *supra* note 23. See also Kesselheim, *supra* note 34; Stewart, DW, Martin, IM. (1994). Intended and unintended consequences of warning messages: A review and synthesis of empirical research. *Journal of Public Policy & Marketing*, 13, 1-19; Byron, MJ, et al. (2016). Adolescents' and adults' perceptions of 'natural', 'organic' and 'additive-free' cigarettes, and the required disclaimers. *Tobacco Control*, 25(5), 517-520.

³⁷ The disclaimers include, “Organic tobacco does NOT mean a safer cigarette” and “No additives in our tobacco does NOT mean a safer cigarette.”

presence of disclaimer statements, research shows they have little to no impact; consumers continue to perceive Natural American Spirit cigarettes as less harmful than other cigarettes.³⁸ Data from the FDA’s Population Assessment of Tobacco and Health (PATH) study also found that 64% of Natural American Spirit smokers inaccurately believed that their brand is less harmful than other brands compared to just 8.3% of smokers of other brands.³⁹

D. There is insufficient evidence that consumers understand how VLN™ cigarettes can reduce nicotine consumption.

It is critical for reduced exposure claims to use plain language that is easy for consumers to understand. One of the applicant’s proposed 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.”⁴⁰ 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.”⁴¹

The likelihood that consumers will be misled by the statement, “Helps reduce your nicotine consumption,” is high. The truth of this statement depends on the extent to which consumers use VLN™ cigarettes in place of NNC cigarettes and not in addition to NNC cigarettes. However, this qualifying information is found nowhere on the pack. Likewise, the truth of the claim “95% less nicotine” depends on whether consumers completely switch and use VLN™ cigarettes exclusively. Without further qualification, 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.”⁴² This confusion even led some participants to question whether the product was intended to function as nicotine replacement therapy (NRT) or as a cigarette.

³⁸ Byron, MJ, 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, SA, 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.

³⁹ Pearson, JL, et al. (2017). Misperceptions of harm among Natural American Spirit smokers: results from wave 1 of the Population Assessment of Tobacco and Health (PATH) study (2013-2014). *Tobacco Control*, 26(e1), e61-e67.

⁴⁰ 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>.

⁴¹ Qualitative Study, *supra* note 30, at 62.

⁴² *Id.*

Dr. Hatsukami, a leading nicotine reduction scientist, expressed similar concerns at the TPSAC meeting. She stated, “I think what's missing here ... is the instruction of completely switching. You know, completely switching, then you'll get the significant reduction in nicotine..”⁴³ She also later noted, “I think one of the gaps is that we really don't know how these smokers are going to use these products when they're given minimal instruction in terms of their use. And so the studies that Dr. Donny and I have conducted were really quite different than what's going to happen on the real marketplace.”⁴⁴

The applicant’s own evidence, along with the shortcomings addressed here and by TPSAC, do not allow FDA to find that consumers will not be misled by the proposed reduced exposure claims. Accordingly, FDA should deny 22nd Century’s MRTP applications.

V. THE VLN™ APPLICATIONS SHOULD BE DENIED FOR INSUFFICIENT EVIDENCE THAT GRANTING SUCH ORDERS WOULD BENEFIT THE HEALTH OF THE POPULATION AS A WHOLE

Cigarettes with lower nicotine levels are not harmless. Nicotine is the primary addictive agent in cigarettes and is not benign. While VLNC cigarettes may be less addictive, the overwhelming health consequences of smoking come from the more than 7,000 chemicals and 69 cancer-causing agents produced from combusted cigarettes.⁴⁵ It is for this reason that VLNC cigarettes remain harmful; indeed deadly.

In order to obtain an exposure modification order, the applicant must demonstrate 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. For VLN™ cigarettes to have a population health benefit, the applicant must demonstrate both that there will be significant uptake of their product among adult smokers, and that such uptake is not offset by: (1) individuals who have never used tobacco products initiating smoking as a result of the claims (addressed in section VI); (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; or (4) individuals who have quit smoking re-initiating with VLN™ cigarettes as a result of the claims.

As outlined below, the applications should be denied because the applicant has failed to demonstrate an expected population health benefit from the availability of VLN™ cigarettes with the proposed claims.

- A. The availability of VLN™ cigarettes with reduced exposure claims will not derive the same benefits as a nicotine product standard.

⁴³ TPSAC Meeting Transcript, at 198.

⁴⁴ *Id.* at 296.

⁴⁵ U.S. Department of Health and Human Services (HHS), *The Health Consequences of Smoking—50 Years of Progress, A Report of the Surgeon General*, 2014.

Absent a reduced nicotine product standard, NNC cigarettes will continue to be readily available and aggressively marketed. This is the reality in which FDA must assess the subject applications. There is no strong evidence that VLNC cigarettes 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.”⁴⁶ This conclusion was echoed by FDA in its PMTA Scientific Review: “The low subjective appeal, along with increased craving and withdrawal, may prevent current smokers from fully transitioning to VLN™ cigarettes.”⁴⁷

It is also important to note that in experimental studies using VLNC cigarettes, participants are generally instructed to exclusively smoke the experimental cigarettes and discouraged from using NNC cigarettes, in order to mimic the conditions of a product standard. Participants are also given payment for participation and a free supply of VLNC cigarettes. Even in these circumstances, exclusive use compliance is low. Dr. Hatsukami, a leading expert on nicotine reduction science, echoed concerns that much of the body of research on reduced nicotine cigarettes is not applicable to the context in which regular nicotine cigarettes continue to be available, stating that “I don’t think you can really generalize the research that we conducted into what might happen if you have both types of cigarettes on the market.”⁴⁸ Still, the applicant’s population modeling assumed 100% of users of its VLN™ cigarettes would “not regress back to conventional cigarette smoking because there would be no conventional cigarettes available”; that is, they “took basically the assumptions of enactment of the proposed rule and ran it through [their] model.”⁴⁹ These conditions are not reflective of the cigarette marketplace in which VLN™ cigarettes will be introduced, though, and thus, the applicant’s population modeling cannot be relied upon.

The low subjective appeal of VLN™ cigarettes, lack of compliance in experimental studies, and evidence from the failed commercial launches of other VLNC cigarette brands, such as Philip Morris’s “Next” cigarette, suggest that uptake of the subject products is likely to be significantly lower than if a nicotine product standard were implemented.⁵⁰

B. There is insufficient evidence that adult smokers will completely switch to VLN™ cigarettes.

⁴⁶ HHS, Office of the Surgeon General, *Smoking Cessation: A Report of the Surgeon General*, 2020.

⁴⁷ FDA, *supra* note 20, at 68.

⁴⁸ TPSAC Meeting Transcript, at 150.

⁴⁹ *Id.* at 89.

⁵⁰ 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.

The FDA’s PMTA Scientific Review concluded that, “Overall, it is anticipated that uptake of VLN™ cigarettes without any claims would be low.”⁵¹ Smokers are unlikely to completely substitute NNC cigarettes for VLN™ cigarettes because VLNC cigarettes have low subjective appeal. However, the population health modeling submitted by the applicant assumes a 25% market penetration.⁵² The applicant presents no evidence to support this market penetration estimate. The low subjective appeal of VLN™ cigarettes and market failure of other VLNC cigarette brands suggest this is entirely unrealistic.⁵³ A research-based assessment of the expected market penetration of VLN™ cigarettes is a critical input to the population health model and to the determination of whether the availability of the subject products will benefit the public health. Without meaningful uptake among adult smokers, there can be no possible benefit to the public health.

If the marketing of VLN™ cigarettes with reduced 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 switching or cessation, there is unlikely to be a substantial population health benefit. There was widespread agreement among TPSAC members that dual use will be a likely outcome for adult smokers who try using VLN™ cigarettes.⁵⁴ Experimental studies, including those submitted by the applicant, demonstrate low compliance rates and high levels of substitution with NNC cigarettes. Dual use will be significantly more likely when smokers are not receiving the product for free, paid to participate in a study, and instructed to exclusively use VLN™ cigarettes.

Dual use behavior is also consistent with data on use of alternative tobacco products. For example, even though some e-cigarettes can deliver equivalent nicotine to conventional cigarettes, most adult users do not switch completely to e-cigarettes. About half (49.6%) of adult e-cigarette users are also current cigarette smokers (dual users).⁵⁵ Dr. King of the CDC echoed these concerns at the TPSAC meeting, noting that, “If you look at e-cigarettes in the market, the people who are quitting using those products are using them more frequently or using products that deliver the nicotine more efficiently. So, you have enough to replace what you otherwise would have gotten from a combustible cigarette. And in this case you're not going to get that. And so, the likelihood of transitioning exclusively, it's going to be very difficult in an environment where you have other products available.”⁵⁶

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. Several U.S. Surgeon

⁵¹ FDA, *supra* note 20, at 68.

⁵² 22nd Century MRTP Application Section VIII. Scientific Studies and Analyses F. Population Modeling – Effect on the Population as a Whole.

⁵³ TPSAC member, Dr. Warner, commented at the TPSAC meeting that 25 or 30 percent market penetration would be “pretty impressive,” which in tandem with, “congratulations if you could do [that],” suggests such an estimate would be quite an achievement. TPSAC Meeting Transcript, at 88.

⁵⁴ TPSAC Meeting Transcript, at 203.

⁵⁵ HHS, *supra* note 46.

⁵⁶ TPSAC Meeting Transcript, at 202.

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.⁵⁷ 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."⁵⁸ Similarly, Dr. Miller of the FDA presented research to TPSAC that a reduction in cigarettes per day of at least 50% can reduce some smoking-related morbidity; however, she concluded that, "It's unclear from the available literature what proportion of smokers who use VLNC cigarettes will reduce their cigarettes per day by at least 50 percent. Thus, the magnitude of the reduction in other morbidities remains unclear."⁵⁹ In regards to mortality, she summarized that, "In general, studies of different populations have not consistently demonstrated that a reduction in cigarettes per day reduces all-cause mortality."⁶⁰ Without complete switching, a population health benefit is not certain.

C. The availability of VLNTM cigarettes with reduced exposure claims could hinder or delay cessation efforts.

The availability of VLNTM cigarettes with reduced exposure claims will also negatively affect the health of the population if the reduced exposure claims would hinder or delay cessation efforts by attracting adult smokers who would otherwise quit, perhaps using safer, FDA-approved cessation methods. As noted in FDA's PMTA Scientific Review, "Using VLNTM King and VLNTM 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."⁶¹

In addition, certain sub-populations in the United States use NNC menthol cigarettes at high rates. This is particularly true among African Americans as 85% of African American smokers use menthol cigarettes (compared to only 29% of White smokers), including seven out of ten African American youth smokers.⁶² The FDA has concluded that NNC menthol cigarettes are "likely associated with increased dependence" and "likely associated with reduced success in

⁵⁷ HHS, *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease*, 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; 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.

⁵⁸ 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>.

⁵⁹ TPSAC Meeting Transcript, at 125-26.

⁶⁰ *Id.* at 126.

⁶¹ FDA, *supra* note 20, at 7.

⁶² Villanti, AC, et al., "Changes in the prevalence and correlates of menthol cigarette use in the USA, 2004–2014," *Tobacco Control*, published online October 20, 2016.

smoking cessation, especially among African American menthol smokers.”⁶³ If VLN™ Menthol King cigarettes caused African American smokers to switch or engage in dual use of VLN™ Menthol King and NNC cigarettes because they perceived the risk to be lower rather than quitting smoking altogether, it would result in a net negative for public health.

The applicant’s consumer perception study raises concern that the reduced exposure claims 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?”⁶⁴ This finding suggests that some may view the subject products, even with the proposed claims and disclaimer, as an NRT, which could prolong cigarette smoking among those seeking cessation products like NRT. These misperceptions are dangerous, with real consequences for public health.

Finally, the applicant’s Quantitative Study provides early evidence that the proposed claims for VLN™ cigarettes could lead to reduced quit attempts using safer, FDA-approved cessation aids. In that study, exposure to the proposed MRTP claims among smokers with intention to quit was associated with reduced intentions to use NRT.⁶⁵ If the applicant’s claims do in fact deter smokers with intent to quit from using FDA-approved cessation products, that will result in net public health harm. At the TPSAC meeting, Dr. Hatsukami concluded, “Currently there isn’t any sufficient evidence to indicate that this labeling might have a public health benefit. And, in fact, there might be public health risk.”⁶⁶ For these reasons, the subject applications should be denied.

VI. THE VLN™ APPLICATIONS SHOULD BE DENIED FOR INSUFFICIENT EVIDENCE ON THE INCREASED LIKELIHOOD OF TOBACCO USE INITIATION BY NON-USERS, PARTICULARLY YOUTH

- A. Given the history of youth cigarette smoking and the current crisis of e-cigarette usage, it is vitally important for FDA to require evidence that MRTPs will not increase youth initiation of tobacco products.

The risk of a gateway effect to smoking NNC cigarettes or using other tobacco products discounts any potential benefits of the availability of VLN™ cigarette with reduced exposure claims. The absence of research on this particular issue was a concern noted in FDA’s PMTA Scientific Review: “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.”⁶⁷ While research shows limited abuse liability of VLNC

⁶³ FDA, *Preliminary Scientific Evaluation of the Possible Public Health Effects of Menthol Versus Nonmenthol Cigarettes* (2013).

⁶⁴ Qualitative Study, *supra* note 30, at 19.

⁶⁵ Quantitative Study, *supra* note 31, at 113.

⁶⁶ TPSAC Meeting Transcript, at 297.

⁶⁷ FDA, *supra* note 20, at 59.

cigarettes among youth smokers in experimental settings, in the current marketplace where regular nicotine cigarettes are widely available and aggressively marketed, there is a serious 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. This concern was echoed at the TPSAC meeting. Dr. Hatsukami noted that in the context of a nicotine product standard, there is unlikely to be sustained, regular use among youth, but she could not say the same for the possibility of progression to regular cigarettes when both VLN™ and regular nicotine cigarettes are available.⁶⁸

The current youth e-cigarette epidemic and the current public discourse surrounding youth nicotine addiction also highlight the importance of considering the impact of the availability of VLN™ cigarettes with reduced exposure claims on the youth population. 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.⁶⁹ 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 not 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.⁷⁰ 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. In this context, research is needed to determine whether youth seeking to end their addiction to e-cigarettes, view the “95% less nicotine,” “Helps reduce your nicotine consumption,” and “... greatly reduces your nicotine consumption” claims as vaping cessation claims. Given the existing evidence that youth e-cigarette use may increase risk for smoking initiation,⁷¹ research is needed to determine the appeal of VLN™ cigarettes with modified risk claims among youth e-cigarette users. The absence of such data in the pending application justifies its denial.

B. VLN™ menthol cigarettes present a greater health risk than non-menthol VLN™ cigarettes, particularly for youth.

Special consideration should be given to the impact of reduced exposure claims on VLN™ Menthol King cigarettes in particular, as FDA has already concluded that menthol cigarettes increase youth smoking initiation.⁷² FDA reiterated this concern in its PMTA Scientific Review, stating that, “As menthol in NNC cigarettes facilitates experimentation and

⁶⁸ TPSAC Meeting Transcript, at 168.

⁶⁹ 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.

⁷⁰ Cullen, KA, et al., *e-Cigarette Use Among Youth in the United States, 2019*, *JAMA*, published online November 5, 2019.

⁷¹ National Academies of Sciences, Engineering, and Medicine. 2018. *Public health consequences of e-cigarettes*. Washington, DC: The National Academies Press.

⁷² FDA, *supra* note 63.

progression to regular smoking, it is unknown to what degree smoking VLN™ Menthol King cigarettes may influence progression to regular smoking compared to NNC menthol cigarettes in new and inexperienced users, particularly youth and young adults.”⁷³ In addition, and as noted above, over 80 percent of African American smokers use menthol cigarettes,⁷⁴ and therefore ending initiation with menthol cigarettes among African American youth is a public health priority. The FDA should deny the MRTP application for VLN™ menthol cigarettes because the applicant provided no research on how the proposed MRTP claims for menthol cigarettes could impact the likelihood of initiation among youth.

- C. Without justification, 22nd Century has failed to present evidence on youth perceptions of the proposed modified risk claims.

The consumer perception and consumer behavior studies submitted by 22nd Century do not address the potential impact on youth, which precludes a sufficient FDA assessment of the reduced exposure claims and their impact on the health of the population as a whole. The FDA cannot have a complete picture of the potential public health impact without reliable youth data. These types of evaluations must be done before MRTPs are authorized by FDA, not just in post-marketing surveys and evaluations. Both FDA’s Draft Guidance for the preparation of MRTP applications (FDA MRTP Draft Guidance) and the Institute of Medicine’s report, *Scientific Standards for Studies on Modified Risk Tobacco Products* (IOM MRTP Report), recommend 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.⁷⁵

Because perceptions of, and intentions to use, a given MRTP are likely to differ by age group, the IOM noted that it is “critical that [MRTP] studies include participants in the following age groups: children (≤ 12 years old), adolescents (13–17 years old), young or emerging adults (18–25 years old), adults (≥ 25 years old).”⁷⁶ The IOM also stated, “adolescents’ perceptions of the risks and benefits of cigarette smoking play an important role in adolescents’ decisions to smoke. 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.”⁷⁷

The failure by 22nd Century to provide any evidence of the effect of the proposed MRTP claims on adolescent risk perception is an inexplicable omission, against not only FDA’s express instructions, but contrary to the statute as well. The consideration of 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

⁷³ FDA, *supra* note 20, at 8.

⁷⁴ Villanti, *supra* note 62.

⁷⁵ FDA, *supra* note 8, at 20; IOM MRTP Report, December 2011, at 165.

⁷⁶ IOM MRTP Report, *supra* note 75, at 174.

⁷⁷ *Id.* at 165.

played—and continues to play—in the recruitment of long-term adult smokers.⁷⁸ This concern was also raised by multiple TPSAC members. For example, Dr. Warner stated that, “I think a major failing of the consumer perception data is that we don’t have any consumer perception data regarding how consumers respond to the ads that we have seen, along with the name Moonlight.”⁷⁹ Ms. Herndon echoed this concern, stating, “It does very much concern me that there’s no evidence that this application thought about testing this with young people, at the age of initiation, and including perceptions of risk.”⁸⁰ The total absence of data on youth perception of VLN™ cigarettes, with the proposed reduced exposure claims, should—standing alone—preclude granting 22nd Century’s applications.

As relevant here, the Tobacco Control Act requires the applicant to enable FDA to find that its reduced exposure claims are “expected to benefit the health of the population *as a whole*” for the agency to issue an exposure modification order (emphasis added).⁸¹ The FDA cannot make this determination without evidence about youth, a key demographic the law sought to protect. Any argument that FDA’s Draft Guidance for the preparation of MRTP applications prevents companies from conducting studies about youth perceptions is simply wrong. The Draft Guidance states only that “study subjects *receiving tobacco products* [should be] current daily tobacco product users at least 21 years of age.”⁸² (emphasis added). Thus, this limitation is not applicable to studies of promotional material such as modified risk claims to determine the effect of such materials on adolescent risk perception or interest in using the product.

The FDA MRTP Draft Guidance also makes clear that inclusion of the effect on adolescent perception should be an essential feature of studies examining potential tobacco use initiation. It 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:

- The likelihood that consumers who have never used tobacco products, *particularly youth and young adults*, will initiate use of the tobacco product (emphasis added).⁸³

⁷⁸ HHS, *supra* note 57, at 530-41, 603-27, and sources cited therein; *U.S. v. Philip Morris*, 449 F. Supp. 2d at 561-691.

⁷⁹ TPSAC Meeting Transcript, at 169.

⁸⁰ *Id.* at 162.

⁸¹ Section 911(g)(2)(B)(iv).

⁸² FDA MRTP Draft Guidance, at 29.

⁸³ *Id.* at 20.

Moreover, the FDA MRTP Draft Guidance instructs companies to “estimate the attributable risk of all of the various health effects for various types of individuals in the U.S. population, as well as the total number of individuals of each type.”⁸⁴ It goes on to state, “The types of individuals may include, but are not limited to, the following ... Non-users who initiate tobacco use with the proposed product, *such as youth*, never users, [and] former users” (emphasis added).⁸⁵

Thus, far from prohibiting the testing of such messages on adolescents, the FDA characterizes such testing as particularly important. In this light, 22nd Century’s failure to provide any evidence of the effect of these messages on adolescent risk perception is an inexplicable omission that ignores FDA’s specific instruction to include that analysis, including a description of how such youth consumer perception research should be done. Recognizing that research among non-smokers, and non-smoking youth in particular, requires care, FDA offers 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.⁸⁶

Similarly, the IOM MRTP Report detailed ideas for how research on youth perceptions of MRTP risks could be conducted consistent with ethical standards of research.⁸⁷ For example, IOM suggests that such research could be appropriately done under the supervision of an independent third party.⁸⁸ Appropriately safeguarded, third-party administered research would make it possible for an applicant to develop reliable evidence regarding the effect of marketing of a product on this key population. The 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.”⁸⁹

Despite the express instructions in FDA’s MRTP Draft Guidance and the extensive discussion in the IOM MRTP Report on how research on youth risk perception could appropriately be conducted, 22nd Century has submitted applications that ignore the effects of the proposed modified risk claims on youth. Applications that present no evidence on the effect of such claims on youth initiation or perception of risk cannot possibly meet the public health standard.

- D. Data on youth use and perceptions of other reduced nicotine cigarette brands is not a substitute for data on VLNTM cigarettes.

While previously marketed reduced nicotine cigarettes like Quest did not show significant uptake among youth, the Quest experience is not entirely generalizable. As CDC’s Dr. King stated

⁸⁴ *Id.* at 22.

⁸⁵ *Id.*

⁸⁶ *Id.* at 26.

⁸⁷ IOM MRTP Report, *supra* note 75, at 10.

⁸⁸ *Id.* at 57.

⁸⁹ *Id.* at 52.

at the TPSAC meeting, “I think that it's basically tantamount to comparing a rotary phone to an iPhone 11. I think that it's particularly important to consider the context of the promotion environment. And when Quest was around, you did not have the machine of both mode of delivery of messages, particularly through social media, but also the types of advertisements. And if you look at a Quest ad, it's nothing like these, what I would call borderline saucy, salacious images that are being used to promote some of these products, including some of the ones in this packet. So, I think it's important to consider also the broader environmental context. And to that end, I'm not convinced that the Quest comparison is entirely relevant and apples-to-apples here, in terms of what could happen among youth.”⁹⁰

The continued lack of any youth data in MRTP applications must end now. The pending 22nd Century applications before FDA provide the agency the opportunity to establish youth perception data as essential to any MRTP. Without such data, 22nd Century has not met the statutory evidentiary obligation required for FDA to authorize its applications.

VII. THE VLN™ APPLICATIONS SHOULD BE DENIED FOR INSUFFICIENT EVIDENCE ABOUT THE IMPACT OF PROPOSED MARKETING MATERIALS

A. The applicant’s proposed marketing materials include youth-friendly imagery.

While 22nd Century states “adult tobacco consumers” are the target of its marketing plan, it is undeniable that its proposed marketing materials include many images of young adult models that depict smoking in a glamorous fashion (See Appendix 2). These images are reminiscent of the major cigarette companies’ advertising, which has been used for decades to attract youth. There is strong empirical evidence that tobacco advertising has a direct impact on the industry’s recruitment of new, youth tobacco users. A key finding of the 2012 Surgeon General Report was the conclusion that there is a causal relationship between the advertising and promotional efforts of the tobacco companies and the initiation and progression of tobacco use among young people.⁹¹ In 2014, the U.S. Surgeon General reiterated this finding, stating that “advertising and promotional activities by the tobacco companies cause the onset and continuation of smoking among adolescents and young adults.”⁹²

Moreover, given the nature of the advertising set forth in Appendix 2, the failure of the applicant to present evidence of the impact of the proposed reduced exposure claims as applied to a product named “Moonlight” is even more problematic. The name “Moonlight” reinforces the seductive messages conveyed by these images far more than the name “VLN” and is likely to enhance the appeal of the product, and the modified exposure claims, to young people. Yet the applicant presented no evidence on the impact on youth of the claims as applied to the product marketed with the Moonlight name.

⁹⁰ TPSAC Meeting Transcript, at 167.

⁹¹ HHS, *supra* note 57.

⁹² HHS, *supra* note 45.

- B. The applicant provided insufficient evidence that they will not expose non-smokers, particularly youth, to their marketing.

In issuing 22nd Century's PMTA orders, FDA required specific restrictions on digital media and digital marketing, including age restrictions for digital sales, websites, and social media, and requirements for tracking and age-gating. However, age-gating on social media is notoriously ineffective. Many social media users are not required to provide an age on their profiles, and if they do, there is no verification process. If 22nd Century were serious about not reaching youth and non-smokers, it would not be advertising on social media – period.

Further, FDA's marketing restrictions have no impact on the applicant's point-of-sale marketing plans. The tobacco industry spends \$9.1 billion a year to market its products throughout the United States, and 96 percent (\$8.7 billion) of that is spent at the point of sale.⁹³ Tobacco industry marketing at the point of sale impacts not only what products and brands kids use, but also the chances that kids will start smoking.⁹⁴ With nearly half of adolescents visiting a convenience store at least once a week,⁹⁵ the chance of a teen being repeatedly and regularly exposed to tobacco marketing is high. In fact, according to the 2019 National Youth Tobacco Survey, retail stores are by far the greatest source of exposure to tobacco advertising among youth. In 2019, eight out of ten (79.4%) middle and high school students reported exposure to tobacco marketing in retail stores.⁹⁶

The VLNTM applications should be denied for insufficient evidence that the applicant's marketing plan will not expose non-smokers—particularly youth—to its marketing.

- C. The applicant did not conduct consumer perception studies using its proposed marketing materials.

The applicant's marketing materials will also influence consumer perceptions about the reduced exposure claims, particularly among non-smokers and youth. Marketing that glamorizes smoking will increase the likelihood that consumers will be misled. However, the applicant only submitted consumer perception studies on the proposed claims 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 must be conducted both with the pack and some representative sample of proposed marketing materials. These concerns were highlighted at TPSAC. For example, Dr. Warner commented that what most concerned him is that “we haven't had any evidence about how people will respond to the

⁹³ U.S. Federal Trade Commission (FTC), *Cigarette Report for 2018*, 2019, <https://www.ftc.gov/system/files/documents/reports/federal-trade-commission-cigarette-report-2018-smokeless-tobacco-report-2018/p114508cigaretterreport2018.pdf> (data for top 5 manufacturers only); FTC, *Smokeless Tobacco Report for 2018*, 2019, <https://www.ftc.gov/system/files/documents/reports/federal-trade-commission-cigarette-report-2018-smokeless-tobacco-report-2018/p114508smokelesstobaccoreport2018.pdf> (data for top 5 manufacturers only).

⁹⁴ HHS, *supra* note 57.

⁹⁵ Sanders-Jackson, A, et al., “Convenience store visits by US adolescents: Rationale for healthier retail environments,” *Health & Place* 34:63-66, 2015.

⁹⁶ 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.

advertising that should be anticipated here. Which, actually, I think is a major flaw in the consumer perception data that we've been given."⁹⁷

As noted previously, the sample marketing materials submitted display the reduced exposure claims in significantly larger font than the disclosure statement, increasing the likelihood that the disclosure statement will be ignored and consumers will be misled (See Appendix 1). Further, the marketing outline and image library submitted by the applicant include imagery with young models in situations that glamorize smoking, which could attract non-tobacco users, including youth (See Appendix 2).

An application that presents no evidence on the effect of reduced exposure claims in its proposed marketing cannot meet the public health standard. The applications should be denied due to insufficient evidence. 22nd Century's marketing will not mislead consumers and not attract youth.

Respectfully submitted,

American Academy of Pediatrics

American Cancer Society Cancer Action Network

American Heart Association

American Lung Association

Campaign for Tobacco-Free Kids

Truth Initiative

⁹⁷ TPSAC Meeting Transcript, at 159-60.

Appendix 1: Disclaimer Statement in Marketing is Absent or in Small Font



REAL TOBACCO

VLN™ smells, burns, and tastes like a conventional cigarette, but greatly reduces your nicotine consumption

95% Less Nicotine

VLN

Learn more at vlncigarettes.com

SURGEON GENERAL'S WARNING: Cigarette Smoke Contains Carbon Monoxide.

Nicotine is addictive. Less nicotine does NOT mean safer. All cigarettes can cause disease and death.

IF YOU SMOKE, CONSIDER VLN™

95% LESS NICOTINE

Helps reduce your nicotine consumption

vlncigarettes.com

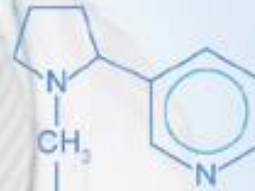


**SURGEON GENERAL'S WARNING:
Cigarette Smoke Contains Carbon Monoxide.**

Image from Section V VLN Marketing Outline

IF YOU SMOKE, CONSIDER VLN™

95%
LESS
NICOTINE



Made with real tobacco, VLN™ smells, burns, and tastes like a conventional cigarette, but greatly reduces your nicotine consumption.

For the nearest retailer,
visit vln-cigarettes.com/stores
or call: 800-225-1838 ext. 221



Nicotine is addictive. Less nicotine does NOT mean safer. All cigarettes can cause disease and death.

**SURGEON GENERAL'S WARNING:
Cigarette Smoke Contains Carbon Monoxide**

**REAL
TOBACCO**



Nicotine is addictive. Less nicotine does NOT mean safer. All cigarettes can cause disease and death.

Switch to

**95%
Less Nicotine**

VLN™ smells, burns, and tastes like a conventional cigarette, but greatly reduces your nicotine consumption

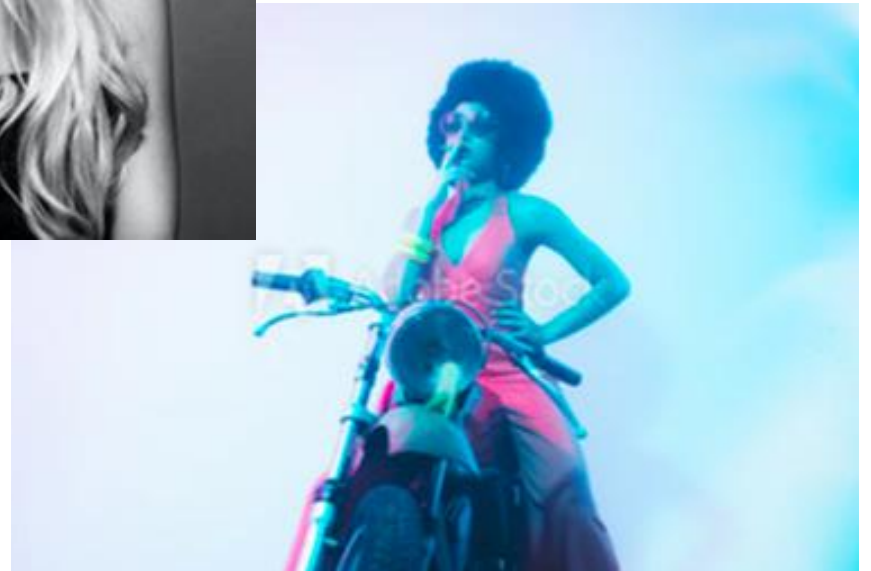
Learn more at
vlncigarettes.com

**SURGEON GENERAL'S WARNING: Cigarette
Smoke Contains Carbon Monoxide.**

Appendix 2: Youth Friendly Marketing



Images from “VLN Image Library Master”



Images from "VLN Image Library Master"

NICOTINE IS ADDICTIVE...
But now, smokers can choose VLN™



95% LESS NICOTINE
Helps reduce your nicotine consumption.

VLN

Nicotine is addictive. Less nicotine does NOT mean safer. All cigarettes can cause disease and death.

95% LESS NICOTINE
REAL TOBACCO

VLN™ smells, burns, and tastes like a conventional cigarette, *but greatly reduces your nicotine consumption.*

For the nearest retailer, visit vncigarettes.com/stores
or call: 800-225-1838 ext. 221

SURGEON GENERAL'S WARNING:
Cigarette Smoke Contains Carbon Monoxide.

Nicotine is addictive. Less nicotine does NOT mean safer. All cigarettes can cause disease and death.

IF YOU SMOKE, CONSIDER VLN™

95% LESS NICOTINE

MADE WITH REAL TOBACCO,
VLN™ SMELLS, BURNS, AND
TASTES LIKE A CONVENTIONAL
CIGARETTE, BUT GREATLY
REDUCES YOUR NICOTINE
CONSUMPTION

Nicotine is addictive. Less nicotine does NOT mean safer. All cigarettes can cause disease and death.

VLN

For the nearest retailer, visit vncigarettes.com/stores
or call: 800-225-1838 ext. 221

SURGEON GENERAL'S WARNING:
Cigarette Smoke Contains Carbon Monoxide.

Image from Section V VLN Marketing Outline