Public Submission #5

Stanton A. Glantz, PhD

Professor of Medicine

Truth Initiative Distinguished Professor of Tobacco Control

Director, Center for Tobacco Control Research and Education

and

Lauren K. Lempert, JD, MPH

Law and Policy Specialist

Center for Tobacco Control Research and Education

Hunter-Thomas, Serina

From: Glantz, Stanton A <Stanton.Glantz@ucsf.edu>
Sent: Friday, February 7, 2020 5:50 PM
To: Zeller, Mitchell
Cc: Holman, Matthew R; Hunter-Thomas, Serina; Lempert, Lauren
Subject: VLM PMTA
Attachments: Zeller letter re VLN PMTA.pdf

February 7, 2020

Mr. Mitchell Zeller
Director, Center for Tobacco Products
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
VIA EMAIL

Dear Mr. Zeller,

FDA issued marketing orders for 22nd Century's Moonlight and Moonlight Menthol reduced nicotine cigarettes on December 17, 2019 based on premarket tobacco product applications (PMTAs) that used the names "VLN King and VLN Menthol King." On October 2, 2019, 22nd Century submitted an amendment to its PMTAs changing the names of the subject cigarettes from "VLN" to "Moonlight" after FDA had already conducted its scientific review using the "VLN" names. Therefore, none of the evidence before FDA when it considered the PMTAs used the Moonlight names that 22nd Century is now authorized to use when it brings these products to market.

As we describe in detail in the attached comment that we submitted to both TPSAC and the docket for 22nd Century's MRTP applications, FDA erred in authorizing the marketing of Moonlight and Moonlight Menthol cigarettes because these product names were not considered by FDA in its scientific review.

The product name is critical to a determination as to whether a product is "appropriate for the protection of the public health" under Tobacco Control Act section 910(c)(4) because the name may well influence whether it is more likely than not that nonusers of tobacco products will initiate with the product, and/or whether it is more likely than not that current users of tobacco products will quit. This is particularly true for the product name "Moonlight" that includes the explicitly prohibited descriptor "light."

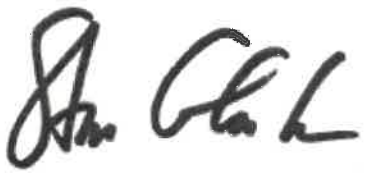
After 22nd Century amended its PMTAs to change the product name to "Moonlight," FDA should have immediately suspended its review of the product until 22nd Century provided a complete application that fully addresses the public health implications of the new name. More important, FDA should withdraw the marketing order for Moonlight and Moonlight Menthol cigarettes under Tobacco Control Act section 910(d)(1)(A) because the continued marketing of this product using a name that was not studied is no longer appropriate for the protection of the public health.

The name change from "VLN" to "Moonlight" is especially relevant to the MRTP applications. To demonstrate that a product should be awarded a reduced exposure MRTP order, Tobacco Control Act section 911(g) requires that the applicant demonstrate consumer understanding of the product's harmfulness or exposure based on the label, labeling, and advertising. Because the MRTP applications were based on studies using a different name ("VLN" instead of "Moonlight," which is what the actual labeling and advertising would use if the MRTP order were granted), the applications should be rejected outright and FDA must not issue a MRTP order.

The name "Moonlight" is especially troublesome since its contains the descriptor "light" which is explicitly prohibited in the law's MRTP provisions, Tobacco Control Act section 911(b)(2)(A)(ii). Indeed, in explaining the intent of the MRTP provisions in the Findings section of the Tobacco Control Act, Congress referred to the federal court decision in the RICO case (*USA v. Philip Morris*) and declared that the term "light" was inherently deceptive and misled consumers to believe that products labeled "light" were less harmful than other products. The law is clear and unambiguous: FDA must not authorize a company to sell any product with the term "light" in its name and labeling, and must not authorize a company to sell such a product with modified risk or exposure claims.

For these reasons, FDA should withdraw its marketing order for Moonlight and Moonlight Menthol cigarettes and should reject 22nd Century's MRTP application to sell these cigarettes with reduced exposure claims.

Best wishes,



Stanton A. Glantz, PhD
Professor of Medicine
Truth Initiative Distinguished Professor of Tobacco Control
Director, Center for Tobacco Control Research and Education

Lauren K. Lempert, JD, MPH
Law and Policy Specialist
Center for Tobacco Control Research and Education

cc: Dr. Matthew R. Holman, Director, Office of Science
Members of the Tobacco Products Scientific Advisory Committee, c/o Serina Hunter-Thomas

Stanton A. Glantz, PhD
Professor of Medicine (Cardiology)
Truth Initiative Distinguished Professor of Tobacco Control
Director, Center for Tobacco Control Research and Education
University of California San Francisco
415-476-3893
Stanton.Glantz@ucsf.edu
http://profiles.ucsf.edu/stanton.glantz
https://tobacco.ucsf.edu/blogs/sglantz
https://tobacco.ucsf.edu
@ProfGlantz

UNIVERSITY OF CALIFORNIA SAN FRANCISCO

BERKELEY • DAVIS • IRVINE • LOS ANGELES • MERCED • RIVERSIDE • SAN DIEGO • SAN FRANCISCO

SANTA BARBARA • SANTA CRUZ

STANTON A. GLANTZ, PhD
Professor of Medicine (Cardiology)
Truth Initiative Distinguished Professor of Tobacco Control
Director, Center for Tobacco Control Research and Education

530 Parnassus Suite 366
San Francisco, CA 94143-1390
Phone: (415) 476-3893
Fax: (415) 514-9345
stanton.glantz@ucsf.edu

February 7, 2020

Mr. Mitchell Zeller
Director, Center for Tobacco Products
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
VIA EMAIL

Dear Mr. Zeller,

FDA issued marketing orders for 22nd Century's Moonlight and Moonlight Menthol reduced nicotine cigarettes on December 17, 2019 based on premarket tobacco product applications (PMTAs) that used the names "VLN King and VLN Menthol King." On October 2, 2019, 22nd Century submitted an amendment to its PMTAs changing the names of the subject cigarettes from "VLN" to "Moonlight" after FDA had already conducted its scientific review using the "VLN" names. Therefore, none of the evidence before FDA when it considered the PMTAs used the Moonlight names that 22nd Century is now authorized to use when it brings these products to market.

As we describe in detail in the attached comment that we submitted to both TPSAC and the docket for 22nd Century's MRTP applications, FDA erred in authorizing the marketing of Moonlight and Moonlight Menthol cigarettes because these product names were not considered by FDA in its scientific review.

The product name is critical to a determination as to whether a product is "appropriate for the protection of the public health" under Tobacco Control Act section 910(c)(4) because the name may well influence whether it is more likely than not that nonusers of tobacco products will initiate with the product, and/or whether it is more likely than not that current users of tobacco products will quit. This is particularly true for the product name "Moonlight" that includes the explicitly prohibited descriptor "light."

After 22nd Century amended its PMTAs to change the product name to "Moonlight," FDA should have immediately suspended its review of the product until 22nd Century provided a complete application that fully addresses the public health implications of the new name. More important, FDA should withdraw the marketing order for Moonlight and Moonlight Menthol cigarettes under Tobacco Control Act section 910(d)(1)(A) because the continued marketing of this product using a name that was not studied is no longer appropriate for the protection of the public health.

The name change from "VLN" to "Moonlight" is especially relevant to the MRTP applications. To demonstrate that a product should be awarded a reduced exposure MRTP order, Tobacco Control Act section 911(g) requires that the applicant demonstrate consumer understanding of the product's harmfulness or exposure based on the label, labeling, and advertising. Because the MRTP applications were based on studies using a different name ("VLN" instead of "Moonlight," which is what the actual labeling and advertising would use if the MRTP order were granted), the applications should be rejected outright and FDA must not issue a MRTP order.

The name "Moonlight" is especially troublesome since its contains the descriptor "light" which is explicitly prohibited in the law's MRTP provisions, Tobacco Control Act section 911(b)(2)(A)(ii). Indeed, in explaining the intent of the MRTP provisions in the Findings section of the Tobacco Control Act, Congress referred to the federal court decision in the RICO case (*USA v. Philip Morris*) and declared that the term "light" was inherently deceptive and misled consumers to believe that products labeled "light" were less harmful than other products. The law is clear and unambiguous: FDA must not authorize a company to sell any product with the term "light" in its name and labeling, and must not authorize a company to sell such a product with modified risk or exposure claims.

For these reasons, FDA should withdraw its marketing order for Moonlight and Moonlight Menthol cigarettes and should reject 22nd Century's MRTP application to sell these cigarettes with reduced exposure claims.

Best wishes,

Stanton A. Glantz, PhD
Professor of Medicine
Truth Initiative Distinguished Professor of Tobacco Control
Director, Center for Tobacco Control Research and Education

Lauren K. Lempert, JD, MPH
Law and Policy Specialist
Center for Tobacco Control Research and Education

cc: Dr. Matthew R. Holman, Director, Office of Science
Members of the Tobacco Products Scientific Advisory Committee, c/o Serina Hunter-Thomas

22nd Century's VLN cigarettes marketing with modified exposure claims has not been tested and will likely be appealing to youth and young adults

Lucy Popova, PhD*; Bonnie Halpern-Felsher, PhD; Benjamin Chaffee, DDS, MPH, PhD; Lauren K. Lempert, JD, MPH; Stanton A. Glantz, PhD

University of California San Francisco TCORS
*Georgia State University

Docket Number: FDA-2019-N-0001

February 7, 2020

On February 14, 2020, TPSAC will convene to discuss 22nd Century's Modified Risk Tobacco Product (MRTP) application requesting exposure modification orders for its VLN King and VLN Menthol King cigarettes. 22nd Century seeks an MRTP order to sell its products with reduced exposure claims, but not reduced harm claims. Its three claims are:

(1) "95% less nicotine"

(2) "Helps reduce your nicotine consumption"

(3) "… greatly reduces your nicotine consumption"

While these three claims were tested when shown on the packs, they have not been tested when shown on print or social media advertisements. Because **the proposed VLN advertisements with modified exposure claims were not tested and have the potential to attract non-smoking youth and young adults, the 22nd Century's MRTP application for VLN cigarettes should be denied.**

As part of the application, 22nd Century submitted VLN Image Library Master_RIF.pdf. ***These advertising images were not tested in the consumer perception studies***. The studies only showed participants packs of the VLN products with the claims on them. On print or online advertisements, where claims of reduced nicotine exposure are combined with aspirational pictures of people enjoying smoking (Figure 1[1]), the same claims might have completely different effects than when shown on the packs.

[1] VLN Cigarettes: Labels, Labeling, and Advertising. Retrieved from Section V: Labels, Part 1. https://syndication-files.s3.amazonaws.com/mrtpa/22century/Posting%20%233/5%20Section%20V%20Part%201%20-%20Labels.zip

Figure 1. Examples of print advertisements for VLNC.

Furthermore, the images that were submitted as proposed marketing glamorize and normalize smoking and tobacco (Figures 2 and 3[2]). Many feature young adults and are reminiscent of JUUL social media marketing, which has been clearly shown to influence youth initiation and use of Juul.[3] It is possible that ***seeing these advertisements will make the VLN products appear more appealing to youth and young adults***.

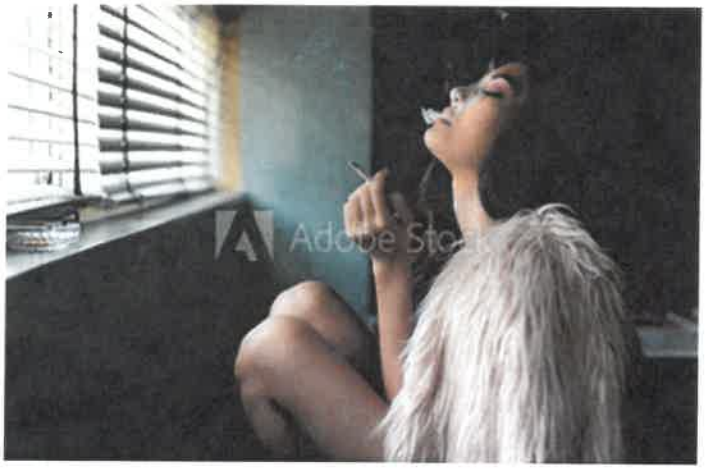


Figure 2. An image from VLN image library to be used in advertising for VLN.

[2] VLN Image Library. Retrieved from Amendments – updated January 28, 2020. https://digitalmedia.hhs.gov/tobacco/hosted/mrtpa/22century/posting5/May%2023%2C%202019%20Amendment.zip

[3] Jackler, R. K., Chau, C., Getachew, B., Whitcomb, M., Lee-Heidenreich, J., Bhatt, A., & Ramamurthi, D. (2019). JUUL advertising over its first three years on the market. SRITA White Paper.

Figure 3. An image from VLN image library to be used in advertising for VLN.

The effects of these advertisements (especially on youth and young adults) have not been tested and this application did not consider the potential uptake by these groups as a result of these advertisements.[4] This missing aspect of the application is critical, given that we have ample evidence showing the direct influence of ads on youth tobacco uptake.

Some proposed advertisements in the application use imagery such as green tobacco plants, sunshine, and words "real tobacco." (Figure 4[5]) This is similar to "implied" health claims used in Natural American Spirit cigarettes, which make consumers perceive these cigarettes as less harmful in absence of explicit modified risk claims.[6]

Because the advertisements that are proposed to be used with the modified exposure claims have not been tested and because the imagery will likely further mislead consumers into believing this VLN cigarettes are less harmful and might attract youth, the MRTP application should be denied.

Figure 4. Example of a print advertisement with a "Real Tobacco" claim.

[4] Kim, M., Popova, L., **Halpern-Felsher, B.**, Ling, PM. Effects of e-cigarette advertisements on adolescents' perceptions of cigarettes. Health Communication. 2017 Dec 13:1-8. PMID: 29236550. Kim, M., Ling, PM., Ramamurthi, D., **Halpern-Felsher, BL**. Youth's perceptions of e-cigarette advertisements with cessation claims. *Tobacco Regulation Science*. 2019;5(2):94-104.

[5] VLN Cigarettes: Labels, Labeling, and Advertising. Retrieved from Section V: Labels, Part 1. https://syndication-files.s3.amazonaws.com/mrtpa/22century/Posting%20%233/5%20Section%20V%20Part%201%20-%20Labels.zip

[6] Moran, M. B., Brown, J., Lindblom, E., Kennedy, R., Cohn, A. M., Lagasse, L., & Pearson, J. L. (2018). Beyond 'Natural': Cigarette Ad Tactics that Mislead about Relative Risk. Tobacco Regulatory Science, 4(5), 3-19. Moran, M. B., Pierce, J. P., Weiger, C., Cunningham, M. C., & Sargent, J. D. (2017). Use of imagery and text that could convey reduced harm in American Spirit advertisements. Tobacco Control, 26(e1), e68-e70.

22nd Century's MRTP application for its VLN cigarettes should be denied because it does not adequately address how its product would be actually used and because the modified exposure claim misleads consumers to believe this product is less harmful than conventional cigarettes

Neal L. Benowitz, MD; Lauren K. Lempert, JD, MPH; Lucy Popova, PhD*;
Bonnie Halpern-Felsher, PhD; Stanton A. Glantz, PhD

University of California San Francisco TCORS
*Georgia State University

Docket Number: FDA-2019-N-0001

February 6, 2020

On February 14, 2020, TPSAC will convene to discuss 22nd Century's Modified Risk Tobacco Product (MRTP) application requesting exposure modification orders for its VLN King and VLN Menthol King cigarettes. FDA issued a marketing order for VLN on December 17, 2019. On October 2, 2019, 22nd Century submitted an amendment to its PMTA to change the names of the subject cigarettes from "VLN" to "Moonlight" and "Moonlight Menthol." All of the evidence before TPSAC was collected using the VLN names, not the "Moonlight" names.

22nd Century now seeks an MRTP order to sell its products with reduced exposure claims, but not reduced harm claims. Its three claims are:

(1) "95% less nicotine"

(2) "Helps reduce your nicotine consumption"

(3) "… greatly reduces your nicotine consumption"

Allowing the marketing of VLN cigarettes with the proposed modified exposure claims would not be appropriate for the protection of public health as is required by law and will mislead consumers into thinking that these products are less harmful. Further, FDA erred in issuing a marketing order based on studies evaluating a different name for the product. FDA should not compound this error by issuing a MRTP order based on inappropriate data. Therefore, 22nd Century's MRTP application for VLN cigarettes should be denied.

It is significant that FDA's Technical Project Lead's report supporting the marketing order noted that the amendment was submitted after FDA had completed its scientific review of the products. ***The fact that FDA issued a marketing order based on studies using the old name and without considering the implications of the new name on user perceptions and use patterns is a serious problem with the marketing order that makes it even more important that TPSAC recommend that FDA not grant an MRTP order for these products.***

1. The VLN MRTP application does not adequately consider how VLN cigarettes would be *actually used* by consumers.

The Family Smoking Prevention and Tobacco Control Act (TCA) section 911(g) provides that to obtain a MRTP exposure modification order, the applicant must demonstrate to FDA that the subject product, "as it is *actually used* by consumers," will reduce consumers' exposure to a substance. Whether or not 22nd Century's VLN cigarettes do, in fact, deliver 95% less nicotine when comparing one VLN cigarette with one conventional cigarette, the application does not address how VLN would actually be used. That is, it does not provide crucial information to answer the key question: Would consumers completely abandon their usual brand of conventional cigarettes and use VLN exclusively, or would consumers use VLN some of the time, and conventional cigarettes or other full-nicotine tobacco products some of the time?

a) There is no evidence in the MRTP application for VLN that 22nd Century studied how VLN would actually be used by consumers.

It is unclear whether 22nd Century tested how VLN is actually used. Moreover, we could not find evidence that 22nd Century's proposed claims on labels or advertising inform consumers that their exposure to nicotine will only be reduced if they do not use other nicotine products concurrently. Previous launches of low nicotine cigarettes were unsuccessful because consumers did not use low nicotine alternatives exclusively when conventional cigarettes were still available. ***The theory of the promise of low-nicotine cigarettes described by Neal Benowitz and Jack Henningfield[1] and the Advance Notice of Proposed Rulemaking[2] for a rule that would require reduced nicotine levels in cigarettes would only be successful in an environment where high-level nicotine products are not available.***

Indeed, 22nd Century acknowledged (page 23 of the Executive Summary) that users were unlikely to use the product again, and pulled its application for authorization of its VLN predecessor as a drug cessation device (January 28, 2020 amendment, Clinical Studies, part 4.1, dated November 19, 2019, IND 103,589) because the company failed to demonstrate the product's efficacy for cessation.

TPSAC should advise FDA to deny 22nd Century's MRTP application for VLN cigarettes because it does not address actual use as mandated by the TCA.

b) In the real world, there is little evidence that smokers will use this product or any other very low nicotine product exclusively, and there is abundant evidence to the contrary.

---

[1] Benowitz, N. L., and J. E. Henningfield. 1994. "Establishing a Nicotine Threshold for Addiction. The Implications for Tobacco Regulation." *The New England Journal of Medicine* 331 (2): 123–25. https://doi.org/10.1056/NEJM199407143310212

[2] FDA, Tobacco Product Standard for Nicotine Level of Combusted Cigarettes, Advance Notice of Proposed Rulemaking, 83 FR 11818, March 16, 2018. Available at: https://www.govinfo.gov/app/details/FR-2018-03-16/2018-05345

To be effective for harm reduction, full-nicotine cigarettes must not be available to smokers. In clinical trials of VLN cigarettes among smokers who were not trying to quit, non-adherence to smoking VLN cigarettes was 80% or higher.[3] That is, while participants did smoke VLN cigarettes as part of the study, they also smoked some regular cigarettes each day. Participants did not find the cigarettes satisfying, and sought nicotine from other sources. Daily nicotine intake was only reduced by 60%, much less than the extent of nicotine reduction in the tobacco filler (95%). Another study showed that when provided with VLN cigarettes at no cost for 7 months after the study ended, nicotine intake returned to the baseline when smoking regular cigarettes, with no significant increased benefit for quitting.[4]

Consistent with these findings for VLN cigarettes, when other reduced nicotine cigarettes (e.g., Philip Morris's "Next" cigarette) were introduced in the marketplace, they were commercially unsuccessful[5] because if someone is addicted to nicotine, reduced nicotine cigarettes are not satisfying. 22nd Century's own studies also support this conclusion:

- 22nd Century's predecessor VLN product X-22 did not reduce cigarette consumption. 22nd Century began a process to obtain approval under FDA's drug authorities for X-22 cigarettes for smoking cessation. However, their clinical study showed there was no difference in abstinence rates three months after the quit date between X-22 and the control, so development of X-22 was "paused." (See p. 8 of Executive Summary, IND 103,589)
- In the VLN King abuse liability study, subjects were asked if they would "use the product again" after a four-hour *ad lib* use session. Subjects rated VLN 34 (on scale of 0-100, where 0 = "definitely would not" and 100 = "definitely would"), which was even lower than their rating for nicotine gum (rated 59) and their usual brand (rated 95). (see Executive Summary, page 23).
- The abuse liability study also measured craving and urges, and VLN Kings did not suppress craving and urges in abstinent smokers to the same degree as usual brands, and there was no difference between nicotine gum and VLN. This seems to indicate that if a smoker's usual brand were available, smokers would use it if they had cravings or urges. (Executive Summary, page 24)
- The applicant states (in the Executive Summary, p. 25), "More than 50 clinical studies have been conducted on VLNC cigarettes which conclusively demonstrate that continued use of VLN cigarettes results in decreased cigarette consumption, reduction in nicotine absorption, and reduction in other biomarkers of exposure." However, it appears that these were clinical studies in which smokers volunteered to smoke VLN cigarettes that were provided at no cost, and the participants were compensated financially for continuing in the studies. ***Even in this context where participants were incentivized to smoke VLN cigarettes, participants continued to smoke some regular cigarettes each day.***

---

[3] Nardone N, Donny EC, Hatsukami DK, et al. Estimations and predictors of non-compliance in switchers to reduced nicotine content cigarettes. Addiction. 2016;111(12):2208–2216.

[4] Benowitz NL, Nardone N, Dains KM, et al. Effect of reducing the nicotine content of cigarettes on cigarette smoking behavior and tobacco smoke toxicant exposure: 2-year follow up. Addiction. 2015;110(10):1667–1675.

[5] Dunsby J, Bero L. A nicotine delivery device without the nicotine? Tobacco industry development of low nicotine cigarettes. Tob Control. 2004;13(4):362–369. doi:10.1136/tc.2004.007914

c) 22nd Century's proposed modified exposure claim and marketing materials for VLN do not communicate to consumers the need to completely switch to or use VLN cigarettes exclusively.

- Other MRTP applications explicitly addressed the complete substitution to the target product in order to realize any reduced risk or reduced exposure claims. For example, the proposed modified risk claim on Copenhagen snuff reads: "IF YOU SMOKE CONSIDER THIS: Switching completely to this product from cigarettes reduces risk of lung cancer." ***The proposed claims for VLN cigarettes do not include any such language.***
- 22nd Century states that its clinical studies "indicate that VLNC cigarettes can help many cigarette consumers substantially reduce their nicotine and cigarette consumption, therefore bringing broad-based benefits to public health." (Page 21 of Executive Summary of MRTP application). However, ***the application does not discuss whether these studies were done in an environment where higher-content nicotine cigarettes were not also available, or whether smokers were instructed that they needed to use VLN exclusively.***
- ***As a result, consumers will likely be misled into believing that they reduce their nicotine consumption by 95% if they smoke VLN cigarettes*** **occasionally.**

2. VLN cigarettes' reduced exposure claims will mislead consumers to believe that the products are less harmful than conventional cigarettes

To issue a modified exposure order, section 911(g)(2)(B)(iii) requires the applicant to demonstrate that "testing of actual consumer perception shows that, as the applicant proposes to label and market the product, consumers will not be misled into believing that the product— (I) is or has been demonstrated to be less harmful; or (II) presents or has been demonstrated to present less of a risk of disease than 1 or more other commercially marketed tobacco products." ***22nd Century's own data submitted in the application show that consumers will be misled, so FDA should not grant it a modified exposure order.***

As part of the MRTP application, 22nd Century Group conducted a quantitative study to evaluate the effects of the proposed modified exposure claims on consumers' comprehension, risk perception, and intentions to use VLN cigarettes.[6] Participants were Adult Current Smokers, Adult Former Smokers, and Adult Never Smokers. Participants were randomized to 4 conditions: 3 claims conditions (two of which are redacted, so they will be excluded from further review) and a control condition. Participants in the control condition were further split into two groups – one saw VLN without modified exposure claims and one saw a Marlboro Gold brand.

Perceived risk was measured by asking questions about a variety of short-term and long-term health risks. "Critical diseases included" having lung cancer, emphysema, mouth/throat cancer, heart disease; "general health issues" included an earlier death, respiratory infections,

[6] 22nd Century Group, I. (2019). *Quantitative Study to Evaluate VLN™ Hypothetical Product Messages Among U.S. Adult Cigarette Smokers, Adult Former Cigarette Smokers and Adult Never Cigarette Users.* Retrieved from https://digitalmedia.hhs.gov/tobacco/hosted/mrtpa/22century/consumerperceptionreports.zip

aging faster, occasional wheezing, a bad cough that lasts for days, early morning cough, poor gum health, serious illness, other types of cancer, reduced stamina, losing some sense of taste, being physically unfit, sores of the mouth or throat, and frequent minor illnesses.

Overwhelmingly, across all populations and most health risks, ***seeing a modified exposure claim resulted in significantly reduced perceptions of health risk*** compared to seeing either a VLN pack without the claim or a Marlboro Gold pack. (In a few subgroups there were a few health risks where the difference was not significant due to lower power because there were fewer participants in each cell, such as recent quitters.) ***Thus, a modified exposure claim misled consumers into believing that VLN cigarettes were less harmful.***

3. 22nd Century's 11th-hour amendment to its PMTA changing the product's name from "VLN" to "Moonlight" should have disqualified the product from obtaining marketing authorization, and is fatal to its MRTP application because the application only considers the impact of claims using the VLN name.

a) 22nd Century indicates that its VLN product is identical to predecessor reduced nicotine products such as Spectrum and Pare, and the only difference between these products is the name. (see Executive Summary page 11. "The VLN cigarettes (Menthol King and King(non-menthol) cigarettes) are also exactly the same as NRC102 and NRC103 SPECTRUM very low nicotine research cigarettes. They are also exactly the same as the PARE cigarettes that were the subject of the previous applications referenced above. *The only difference between each respective regular or menthol VLN, PARE and SPECTRUM NRC102/NRC103 brand style is the name of the product."* (emphasis added)

b) The fact that the company changed the name of the product while leaving the identical product is evidence that the name of the product itself is very significant to consumer perceptions of the product and possibly ultimately influences the product's effectiveness. Specifically, the name affects the product's ability to convince smokers to use the low-nicotine product instead of their higher-nicotine usual brand cigarettes.

c) To demonstrate that a product should be awarded a reduced exposure MRTP order, TCA section 911(g) requires that the applicant demonstrate consumer understanding of the product's harmfulness or exposure based on the label, labeling, and advertising. ***Because the entire MRTP application was based on studies using a different name (VLN instead of Moonlight, which is what the actual labeling and advertising would use if the MRTP order were granted), the application should be rejected outright and FDA must not issue a MRTP order.***

d) The name "Moonlight" is especially troublesome, since it contains the word "light" which is a descriptor explicitly prohibited in TCA section 911(b)(2)(A)(ii). A federal court (in the RICO case, *USA v Philip Morris*) and Congress found (see TCA section 2 Findings) that the term "light" was deceptive and misled consumers to believe that products labeled "light" were less harmful than other products. (Adolescents in particular

misperceive the health risks associated with "light" cigarettes.[7]) Indeed, these findings were the foundation of the MRTP provisions.

4. 22nd Century's own studies demonstrate and its own statements declare that VLN is *not less harmful than cigarettes.* Therefore, marketing VLN is not "appropriate for the protection of the public health," and FDA should not issue an order permitting VLN to be marketed with MRTP claims. FDA should also withdraw its PMTA marketing order.

a) The MRTP application states that although VLN is not less harmful than cigarettes, it is no more harmful than cigarettes. This admission does not support a finding that VLN is "appropriate for the protection of the public health," which is a necessary finding for both a marketing authorization and authorization to make MRTP claims.
   - "The Company believes VLN cigarettes have the same risks as conventional cigarettes…" (Executive Summary, p. 10)
   - "VLN cigarettes are not considered to be less hazardous than conventional cigarettes…. The Harmful and Potentially Harmful Constituent (HPHCs) in the smoke of VLN cigarettes were similar to those measured in the smoke of the market-leading brands…." (Executive Summary, p. 18)
   - "The Company does not believe that these results demonstrate that the product has reduced risks. The Company does believe that these results demonstrate that it is unlikely that VLN presents an increased risk to the consumer." (Executive Summary, p. 19-20)
   - "… 22nd Century believes that VLN cigarettes are no more hazardous than conventional cigarettes."

b) Based on 22nd Century's own studies and statements, VLN cigarettes are not "appropriate for the protection of the public health" (APPH). To be APPH, it is not enough that a product is no more dangerous than a conventional cigarette.

c) The APPH standard is a necessary requirement for obtaining both a marketing order under the PMTA provisions, and an order to be permitted to make reduced exposure claims under the MRTP provisions.
   - TCA section 911(g)(2)(B)(i) provides that FDA may issue a reduced exposure MRTP order only if FDA finds that "such order would be appropriate to promote the public health."

d) Since 22nd Century did not meet its burden of demonstrating that marketing VLN at all, let alone with reduced exposure claims, is APPH, FDA must deny its MRTP application, not issue a reduced exposure MRTP order, and withdraw its order granting 22nd Century authorization to market VLN/Moonlight.

5. The proposed modified exposure claims for VLN decrease intentions to use NRT among smokers with intentions to quit.

---

[7] Kropp, RY & Halpern-Felsher, BL. Adolescents' beliefs about the risks involved in smoking 'light' cigarettes. Pediatrics. 2004 Oct. 114(4): e445-e451. PMID: 15466070.

In the quantitative consumer perceptions study,[8] intentions to use cigarettes, e-cigarettes, moist snuff, and nicotine replacement therapy (NRT) were measured before and after exposure to the stimuli. For smokers with intention to quit, seeing a VLN pack with the modified exposure claim reduced intentions to use NRT to a greater extent than seeing a control stimulus (VLN pack with no claim or Marlboro Gold).[9] Figure 1 (next page), based on data in the MRTP application, demonstrates that at pretest, participants in all three conditions had roughly the same intentions to use NRT (between 3.6 and 3.8 on a 6-point scale). After the exposure, intentions were reduced in all groups, but while in the control groups the intentions were around 3.4, the intentions in the modified exposure claim condition dropped to 3.1.

In comparison, the same smokers (in the modified exposure claim condition) had greater intent to use VLN cigarettes (3.8 and 4.1 at two time points after the exposure).[10]

These results indicate that VLN with modified exposure claims might reduce quitting among smokers with quitting intentions who might be more likely to seek cessation aid in the VLN cigarettes than in the FDA-approved NRT medications. This will be a population-level harm.

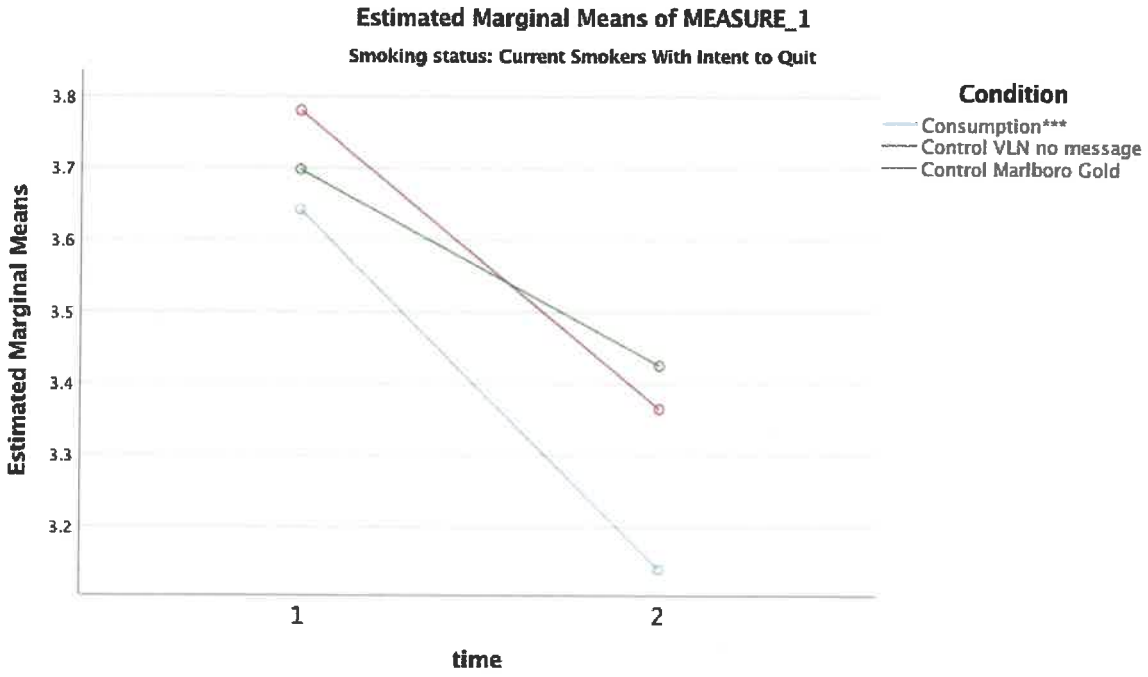
---

[8] 22nd Century Group, I. (2019). *Quantitative Study to Evaluate VLN™ Hypothetical Product Messages Among U.S. Adult Cigarette Smokers, Adult Former Cigarette Smokers and Adult Never Cigarette Users.* Retrieved from https://digitalmedia.hhs.gov/tobacco/hosted/mrtpa/22century/consumerperceptionreports.zip

[9] Unweighted analyses of the raw data provided in the application, file "MARC_QN_Appx_J_RawData_5180080_2018_Datamap_ComaDelim_Release_in_full.xls" in Appendix J, Part 5.31 Scientific Studies - Consumer Perception, available at https://digitalmedia.hhs.gov/tobacco/hosted/mrtpa/22century/posting7/Part%205.31%20Scientific%20Studies%20-%20Consumer%20Perception.zip. Significant time by cell interaction, $F(2, 3074)=8.4$, $p<.001$.

[10] Table 60, p. 113. 22nd Century Group, I. (2019). *Quantitative Study to Evaluate VLN™ Hypothetical Product Messages Among U.S. Adult Cigarette Smokers, Adult Former Cigarette Smokers and Adult Never Cigarette Users.* Retrieved from https://digitalmedia.hhs.gov/tobacco/hosted/mrtpa/22century/consumerperceptionreports.zip

Figure 1. Among smokers with intentions to quit, exposure to modified exposure claim ("Consumption***" condition) reduced intentions to use NRT to a greater extent than exposure to the control packs.[11]



Conclusion:

FDA should deny 22nd Century's MRTP application for its VLN cigarettes and should not issue an order permitting the company to market its Moonlight/VLN cigarettes for the following reasons:

1. The VLN MRTP application does not adequately consider how VLN cigarettes would be *actually used* by consumers as required by the Family Smoking Prevention and Tobacco Control Act. There is no evidence in the MRTP application for VLN that 22nd Century studied the likelihood that VLN smokers would use regular, higher nicotine cigarettes concurrently with VLN.
2. For VLN cigarettes to be effective for harm reduction, full-nicotine cigarettes must not be available to smokers. In clinical trials of VLN cigarettes among smokers who were not trying to quit, non-adherence to smoking VLN cigarettes was 80% or higher.

[11] Unweighted analyses of the raw data provided in the application, file "MARC_QN_Appx_J_RawData_5180080_2018_Datamap_ComaDelim_Release_in_full.xls" in Appendix J, Part 5.31 Scientific Studies - Consumer Perception, available at https://digitalmedia.hhs.gov/tobacco/hosted/mrtpa/22century/posting7/Part%205.31%20Scientific%20Studies%20-%20Consumer%20Perception.zip.

3. 22nd Century's proposed modified exposure claim and marketing materials for VLN do not communicate to consumers the need to completely switch to or use VLN cigarettes exclusively.
4. The proposed modified exposure claims for VLN will mislead consumers to believe that the products are also less harmful than conventional cigarettes. The Tobacco Control Act explicitly requires MRTP applicants to demonstrate that consumers will not be so misled.
5. 22nd Century's 11th-hour amendment to its PMTA changing the product's name from "VLN" to "Moonlight" should have disqualified the product from obtaining marketing authorization, and is fatal to its MRTP application that only considers the impact of claims using the VLN name.
6. The proposed modified exposure claims for VLN decrease intentions to use nicotine replacement therapy among smokers with intentions to quit.

Additionally, FDA erred in issuing a marketing order that would allow 22nd Century to market its reduced-nicotine products with the name "Moonlight," even though all the studies submitted in support of its PMTA application used the name "VLN." Tobacco Control Act section 911(g)(2)(A)(i) provides that FDA may not issue a modified exposure MRTP order unless the applicant has demonstrated that "such order would be appropriate to promote the public health." 22nd Century has not met this burden. ***FDA should rescind that marketing order unless and until 22nd Century submits the necessary evidence to demonstrate that allowing the sale of this product with the names "Moonlight" and "Moonlight Menthol" would be appropriate for the protection of public health.***