

FDA Briefing Document

February 14, 2020

**Meeting of the Tobacco Products Scientific Advisory
Committee**

Modified Risk Tobacco Product Applications (MRPTAs)
MR0000159 – MR0000160
22nd Century Group Inc.

Office of Science
Center for Tobacco Products
Food and Drug Administration

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TABLE OF CONTENTS

DRAFT TOPICS FOR DISCUSSION..... 4

EXECUTIVE SUMMARY 5

INTRODUCTION 8

PRELIMINARY FDA REVIEW FINDINGS 12

REFERENCES..... 233

**APPENDIX A: STATUTORY REQUIREMENTS FOR MODIFIED RISK TOBACCO PRODUCTS (MRTPS) AND
OVERVIEW OF FDA REVIEW PROCESS..... 266**

Draft Topics for Discussion

FDA is reviewing the scientific information submitted in the MRTPAs to determine whether the statutory requirements for authorization provided in Section 911 of the FD&C Act have been met. FDA is also reviewing public comments submitted in accordance with Section 911(e).

FDA intends to raise the following topics for discussion with TPSAC. These topics address the effects of marketing these products with the proposed labeling and advertising, which includes modified risk information and a “voluntary warning.”¹

Preamble: The following discussion questions address the effects of marketing these products with the proposed labeling and advertising, which includes modified risk information and a “voluntary warning.”

1. Discuss whether the labeling enables consumers to accurately understand the following effects of using the products:
 - a. Addiction risk
 - b. Disease risks
2. Discuss the likelihood that reductions in dependence translate into substantial reductions in morbidities and mortality among individual tobacco users.
3. Discuss the extent to which the following groups are likely to try and progress to regularly using the proposed modified risk tobacco products:
 - a. Never smokers
 - b. Former smokers
4. Discuss the extent to which the following groups will dual use the proposed modified risk products with their usual brand of cigarettes or exclusively use the proposed modified risk products:
 - a. Cigarette smokers who want to quit smoking
 - b. Cigarette smokers who do not want to quit smoking

¹ This is the applicant’s term.

Memorandum

Date:	January 15, 2020
To:	Members, Tobacco Products Scientific Advisory Committee
From:	Matthew Holman, Ph.D., Director, Office of Science, Center for Tobacco Products, United States Food and Drug Administration
Subject:	Overview of the FDA Briefing Document for February 14, 2020 discussion of 22 nd Century Group Inc. VLN™ King and VLN™ Menthol King combustible cigarettes (FDA Submission Tracking Number MR0000159-MR0000160)

Executive Summary

22nd Century submitted MRTPAs to market VLN™ King and VLN™ Menthol King combustible cigarettes with three reduced exposure claims:

- “95% less nicotine”
- “Helps reduce your nicotine consumption”
- “greatly reduces your nicotine consumption”

FDA also identified seven additional claims in the submitted proposed advertising, which are similar in content to the three claims listed above.

The two products in this application are similar to Quest and SPECTRUM Very Low Nicotine Content (VLNC) cigarettes, and the applications refer to published research on these VLNC cigarettes. FDA found the two products in this application without modified risk labeling/advertising to be appropriate for the protection of public health on December 17, 2019.² Additionally, the applicant proposes to use the following “voluntary warning”:³

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

² <https://www.fda.gov/media/133635/download>
<https://www.fda.gov/media/133633/download>

³ This is the applicant’s term.

These claims and “voluntary warning” appear on the proposed package label and some of the proposed advertising.

Claim substantiation

FDA’s preliminary scientific review of the application found that the three proposed claims are substantiated: there is about a 95% reduction in nicotine in the tobacco itself, the smoke it yields, and the nicotine that is absorbed when the product is smoked exclusively. When the product is dual used with normal nicotine content cigarettes, nicotine exposure is still significantly reduced. In studies of smokers who do not intend to quit, compared to smokers assigned to a control condition where they continue smoking usual brand cigarettes, smokers assigned to use the product reduce total number of cigarettes per day (CPD) by about 30% at 6 weeks and 50% at 20 weeks.

This document does not discuss the substantiation of the seven additional claims FDA identified because FDA is not seeking specific input from the committee on them.

Consumer perception and understanding

In the applicant’s consumer perception study, consumers assigned to view either VLN™ (with the three modified risk claims and “voluntary warning”) or Marlboro Gold cigarette packs rated the risk of addiction and of getting 18 health conditions from using the product on a 5-point scale (5 = “Very High Risk.”) For both products, mean risk ratings for addiction and the health conditions were moderate to high (3-4 on the 5-point scale). While participants accurately rated VLN™ cigarettes as less addictive than Marlboro Gold cigarettes, it is unclear whether they understood the relative health risks of using the products. They rated their risk of getting all 18 health conditions as significantly lower when using VLN™ cigarettes. If participants assumed they would smoke less of the product than Marlboro Gold when making these ratings, then rating it as lower risk may not reflect a misperception. If participants assumed they would smoke the product in the same way as Marlboro Gold cigarettes, then rating it as lower risk does reflect a misperception. It is unclear what assumptions made when rating these risks.

Morbidity and mortality

The applicant’s study and the peer-reviewed literature indicate that the abuse liability of VLN™ cigarettes is similar to nicotine replacement therapy (NRT) gum. Using VLNC cigarettes can reduce nicotine dependence. In clinical studies, where smokers are told to switch completely to VLNC cigarettes, CPD and nicotine dependence scores decrease even among smokers who continue to dual use the product with their usual brand cigarettes. Reducing cigarette consumption can increase the likelihood that some smokers will quit. Using VLNC cigarettes is associated with increased quit attempts, even among smokers not interested in quitting. Among smokers interested in quitting, switching to VLNC cigarettes in combination with using NRT may also facilitate quitting.

Using these products can substantially reduce dependence; however, the magnitude of the reduction in other morbidities and mortality from reduced dependence remains unclear. Reduction in some morbidities have been found when smokers reduce their CPD by at least 50%. Only one study of VLNC cigarettes has assessed outcomes past 6 weeks; this study found that, over 20 weeks, CPD decreased by about half when comparing between groups (control vs. those told to immediately switch to VLNC cigarettes), but CPD decreased by about a quarter within the VLNC group compared to baseline. We

note that the study was designed to make between-group comparisons, thus rely more on that comparison (finding an approximately 50% reduction).

Impact on nonsmokers and current cigarette smokers

In the consumer perception study, former smokers and never smokers assigned to view VLN™ cigarette packs (with the three modified risk claims and “voluntary warning”) or Marlboro Gold packs. The mean intention to purchase either product was low, and intention to purchase VLN™ cigarettes was significantly higher than intention to purchase Marlboro Gold. There is no direct evidence on how the proposed claims would affect youth, and it is possible that the proposed claims could increase youth product initiation. However, the low abuse liability of VLN™ cigarettes reduces the potential for youth to become addicted regular smokers. In the consumer perception study, smokers assigned to view the VLN™ cigarette packs or Marlboro Gold packs had moderate intentions to use either product, and intentions to use VLN™ cigarettes was significantly higher than intention to purchase Marlboro Gold.

FDA preliminary conclusions

FDA is evaluating the proposed modified risk tobacco products under requirements listed in Section 911(g)(2) of the FD&C Act. FDA’s preliminary conclusions are as follows:

- Substantiation: The three proposed claims are substantiated.
- Consumer understanding: Consumers understand the addiction risk of using the products relative to normal nicotine content cigarettes, but it is unclear whether they understand other relative health risks of using the products; they perceive the products to be lower risk than other cigarettes.
- Morbidity and mortality: The proposed modified risk products can reduce dependence among individual tobacco users. The magnitude of the reduction in other morbidities and mortality from reduced dependence remains unclear.
- Population health impact: Nonsmokers have low intentions to use the products, and current smokers have moderate intentions to use the products. All smoker groups have higher intentions to purchase VLN™ cigarettes compared to Marlboro Gold cigarettes.

Introduction

We would like to thank the TPSAC members in advance for their efforts to provide recommendations to FDA on the Modified Risk Tobacco Product Applications (MRTPAs) submitted by 22nd Century Group Inc. (referred to as “the applicant” in this document).

On May 20, 2019, FDA received MRTPAs from 22nd Century Group Inc. stating that the applicant is seeking exposure modification orders under Section 911(g)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for its VLN™ King and VLN™ Menthol King combustible cigarettes. Appendix A provides additional information on the statutory requirements for Modified Risk Tobacco Products (MRTPs).

The applicant describes VLN™ cigarettes as identical to conventional cigarettes except that they contain VLN™ tobacco. The applicant states that VLN™ tobacco is tobacco that has been “modified/selected” to contain less nicotine than conventional tobacco. Specifically, the applicant states that VLN™ tobacco contains a target level of 0.5 mg of nicotine per gram of tobacco, and this is at least 95% less nicotine than the conventional tobacco used in the top 100 cigarette brands on the market in the United States. VLN™ King and VLN™ Menthol King cigarettes are similar to SPECTRUM NRC 102 (non-menthol) and SPECTRUM NRC 103 (menthol) Very Low Nicotine Content (VLNC) research cigarettes. Both types of cigarettes use identical tobacco filler and have similar nicotine yields, but there are some differences between products (e.g., VLN™ cigarettes have fewer ventilation holes). The applicant refers to peer-reviewed studies of these SPECTRUM cigarettes in its applications.

FDA evaluates all information and statements on the proposed label, labeling, and advertising submitted by the applicant as part of our scientific review. FDA is not seeking specific input from the committee on substantiation of any claims.

The applicant requested to market the products with the following three reduced exposure claims, which appear on the products’ packages (non-menthol example in Figure 1) and advertising (two examples in Figure 2):

- Claim #1: “95% less nicotine”
- Claim #2: “Helps reduce your nicotine consumption”
- Claim #3: “greatly reduces your nicotine consumption”

Additionally, the applicant proposes use of the following “voluntary warning” on the products’ packages and some of the proposed advertising:

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



Figure 1. Images of the front and back of the proposed VLN™ cigarette pack labeling. Images are for the non-menthol product. Pack labeling for the menthol product contains the same modified risk information and “voluntary warning.” Source: Section V “Labels, Labeling, and Advertising,” p. 8.

Figure 2. Example proposed email and print ads. Source: Section V “VLN Marketing Outline,” pp. 13, 15.

FDA also identified the following additional claims and potential claims in the proposed advertising submitted:

- Claim #4: “As a result of our unique technology and plant breeding expertise, VLN™ tobacco grows with 95% less nicotine than conventional tobacco.”
- Claim #5: “Without exception, VLN™ cigarettes contain at least 95% less nicotine than the top 100 cigarette brands in the United States.”
- Claim #6: Several ads display a graph depicting lower nicotine levels of VLN™ cigarettes compared to other cigarette brands.
- Claim #7: “VLN™ cigarettes are substantially lower in nicotine content than any other cigarettes currently available to smokers in the United States. VLN™ cigarette contain an average of just 0.27mg of nicotine.”
- Claim #8: “22nd Century’s VLN™ cigarettes contain an average of .27mg nicotine”
- Claim #9: “VLN™ cigarettes contain .27 +/- 0.1mg nicotine”
- Claim #10: “22nd Century’s VLN™ cigarettes feature the same nicotine content as the lowest nicotine style of the Company’s SPECTRUM research cigarettes.”

FDA notes that the imagery and models in some of the proposed advertising could appeal to youth. However, the applicant did not submit any studies of any of the proposed advertising in the applications. We are not seeking specific input on this from the committee.

FDA is evaluating the products with the proposed claims under the requirements of Section 911(g)(2) of the FD&C Act. FDA is particularly interested in TPSAC’s insights with respect to the following statutory requirements:

- 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
 - is or has been demonstrated to be less harmful; or
 - presents or has been demonstrated to present less of a risk of disease than 1 or more other commercially marketed tobacco products; and
- The scientific evidence that is available without conducting long-term epidemiological studies demonstrates a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies;
- Issuance of orders with respect to the applications 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.

Regulatory History

The following submissions from the applicant were received by FDA on the specified dates:

- May 20, 2019: original MRTPAs.
- May 23, 2019: an amendment containing updates to Section V. Labels, Labeling, and Advertising.
- June 15, 2019: an amendment containing 12-month storage stability and water activity study results.
- July 18, 2019: an amendment containing a new, 6-week clinical study sponsored by the applicant involving 140 subjects evaluating use behavior and biomarkers.
- August 7, 2019: an amendment containing additional medical information on the serious adverse event experience in the 6-week clinical study.
- August 28, 2019: an amendment containing clarification on the stimuli participants viewed in the study's "VLN™ control" condition in the quantitative consumer perception M/A/R/C Research study.
- September 13, 2019: an amendment containing additional clarification on the "VLN™ control" condition in the quantitative consumer perception M/A/R/C Research study.

Preliminary FDA Review Findings

I. Claim substantiation

FDA's preliminary review has found that data from the applicant's studies, the scientific literature, and Southeast Tobacco Laboratories (STL) substantiate the three proposed claims identified by the applicant.

In this section, we describe evidence supporting the three proposed claims identified by the applicant. We do not discuss the substantiation of the seven additional claims FDA identified because FDA is not seeking specific input from the committee on them.

Claim 1: "95% less nicotine"

With respect to the product itself, the reported tobacco nicotine content of all 10 batches of the two new VLN™ tobacco products met their maximum nicotine specification of 0.7 mg/g on a dry weight basis. In addition, their reported nicotine levels in tobacco and nicotine yields in mainstream smoke are at least 96% lower than the majority of the market-leading conventional cigarette brands. Moreover, the Southeast Tobacco Laboratory (STL) test results confirm the very low nicotine amounts and deliveries of the VLN™ cigarettes.

With respect to nicotine exposure from using the product, the literature finds that exclusive use of VLNC cigarettes across five days results in an average 94% reduction in urinary total nicotine equivalents (a biomarker of exposure; Denlinger et al., 2016). Additionally, the applicant's submitted abuse liability studies support that controlled and *ad libitum* use of VLN™ cigarettes in a confined setting results in approximately 97% lower plasma nicotine levels compared to smoking usual brand cigarettes. As such, with exclusive use of VLNC cigarettes, consumers will reduce their exposure to nicotine by approximately 95%.

Claims 2 and 3: "helps reduce your nicotine consumption," "greatly reduces your nicotine consumption"

As described above, exclusive use of this product reduces nicotine exposure by 94-97% (depending on measurement method and study). However, the high rate of non-compliance in clinical studies of VLNC cigarettes suggests that exclusive use of VLNC cigarettes is low (approximately 22% of participants; Nardone et al., 2016). Furthermore, dual use of VLNC cigarettes with other tobacco or nicotine-containing products (e.g., usual brand cigarettes, electronic nicotine delivery systems, NRT) is likely to occur in the open marketplace, particularly as consumers acclimate to smoking VLN™ cigarettes (Hatsukami et al., 2017; Hatsukami et al., 2018). When considering dual use (i.e., non-compliance) with usual brand, normal nicotine content cigarettes, the applicant's 6-week longitudinal study on actual use of VLN™ cigarettes indicates that urinary total nicotine equivalents are reduced by averages of 48% and 58% in participants who switch from usual brand, normal nicotine content cigarettes to VLN™ King and Menthol King cigarettes, respectively. When accounting for non-compliance, published studies report an average 59-60% reduction in nicotine exposure over 6 to 20 weeks of VLNC cigarette use (Nardone et al., 2016; Hatsukami et al., 2018). This indicates that even when the products are used with other nicotine-containing products, nicotine exposure is still substantially reduced compared to exclusive usual brand, normal nicotine content cigarette smoking.

Additionally, the applicant's 6-week longitudinal study and submitted literature review support that switching to smoking VLNC cigarettes leads most cigarette smokers to smoke fewer total (VLNC and

usual brand) cigarettes per day (CPD) compared to ongoing usual brand normal nicotine content cigarette smoking. Studies that evaluated CPD after 6 weeks of smoking VLNC cigarettes report reductions ranging from 11% to 46% (e.g., Donny et al., 2015; Foulds et al., 2018; Pacek et al., 2016; Tidey et al., 2017). By 20 weeks, total CPD among smokers assigned to smoke VLNC cigarettes was about half that of those assigned to smoke normal nicotine cigarettes (Hatsukami et al., 2018). These findings provide further support that use of VLN™ King and Menthol King cigarettes is associated with reduced nicotine consumption. We are not aware of clinical studies of VLNC cigarettes that assess outcomes past 20 weeks.

II. Consumer understanding

This section will inform the following discussion question:

1. *Discuss whether the labeling enables consumers to accurately understand the following effects of using the products:*
 - a. *Addiction risk*
 - b. *Disease risks*

The applicant conducted a quantitative consumer perception study in which it randomized participants to view images of the proposed products' regular and menthol packages (which each include the three claims and "voluntary warning") or a Marlboro Gold cigarette pack. This study did not include advertising. Participants also rated the disease risk of conventional cigarettes before viewing these packages. Participants rated the perceived risk of addiction and perceived risk of 18 other health conditions. They also rated intentions to purchase the product and intentions to use on a regular, ongoing basis (discussed in Section IV).

Consumer understanding of addiction and disease risk

We seek to evaluate whether the proposed labeling would enable consumers to understand that, if smoked in the same way as other cigarettes, VLN™ cigarettes are less addictive, but are not otherwise less harmful.

Prior published research has found that most U.S. adults understand that nicotine is the addictive substance in cigarettes (e.g., O'Brien et al., 2017), but many U.S. adults incorrectly believe that nicotine is also the substance that causes most of the health risks from smoking, such as cancer (Bansal-Travers et al., 2010; Borrelli & Novak, 2007; Mutti et al., 2011; O'Brien et al., 2017). Accordingly, studies have found that U.S. adult smokers perceive low nicotine cigarettes as less likely to cause tobacco-related diseases than other cigarettes, even when smoked at the same rate as other cigarettes (Denlinger-Apte et al., 2017) and when smoked for many years (Byron et al., 2018). Anticipating that some consumers may misinterpret the proposed modified risk claims to mean that VLN™ cigarettes are less harmful than other cigarettes when smoked in the same way, the applicant proposes to include a "voluntary warning" alongside the modified risk claims, stating: "Nicotine is addictive. Less nicotine does NOT mean safer. All cigarettes can cause disease and death."

The applicant's consumer testing found that, after viewing a VLN™ pack with the proposed claims and "voluntary warning," U.S. adult current, former, and never smokers understood that VLN™ cigarettes are less addictive than other cigarettes, but also perceived VLN™ cigarettes to have other lower long-term or lifetime *health risks*, compared to other cigarettes. Specifically, regarding perceived

addictiveness, participants perceived VLN™ cigarettes as less addictive than Marlboro Gold and conventional cigarettes in general: across smoker groups, mean risk ratings were between 0.4 and 1.0 points lower for VLN™ than for Marlboro Gold (on a 5-point scale, 5 = “Very High Risk”), and these differences were statistically significant. Participants still perceived some risk of addiction from smoking VLN™ cigarettes ($M_s = 3-4$ on a 5-point scale). Regarding other perceived health risks, participants perceived VLN™ cigarettes as presenting lower risk of 18 health conditions (e.g., lung cancer, heart disease) than Marlboro Gold and conventional cigarettes, and these differences were all statistically significant. Across health conditions and smoker groups, the mean risk ratings were between 0.3 and 0.7 points lower for VLN™ than for Marlboro Gold (on a 5-point scale). Participants still perceived some risk for getting these health conditions from smoking VLN™ cigarettes ($M_s = 3-4$ on a 5-point scale). Figure 3 below depicts these findings for four health conditions among current smokers intending to quit; differences were largest in this group but were in the same direction and also statistically significant among never smokers, former smokers, and current smokers not intending to quit.

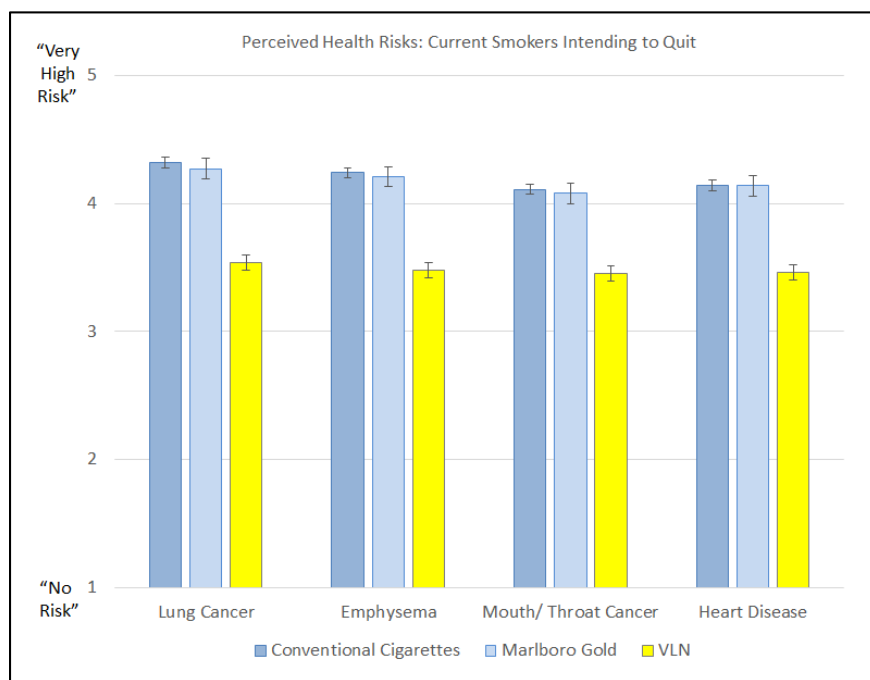


Figure 3. Perceptions of health risks from using conventional cigarettes, Marlboro Gold, and VLN™ after viewing the VLN™ labeling with the proposed modified risk information, among current smokers intending to quit. The study item asked, “Taking into consideration everything you know about [product], indicate what you believe is the risk of each of the following long-term or lifetime health-related issues because of smoking [product].” Source: Based on data in the M/A/R/C Research Quantitative Report. Error bars: 95% CIs.

Our ability to determine whether the above findings reflect an accurate understanding of the disease risks of smoking VLN™ cigarettes is limited, because we do not have information on what assumptions participants made when rating product health risks. We considered two scenarios: that participants assumed they would use VLN™ cigarettes the same amount as other cigarettes when rating the products, or that participants assumed they would use less of VLN™ cigarettes compared to other cigarettes when rating the products. If participants assumed that they would use VLN™ cigarettes the same way as other cigarettes, then their rating of VLN™ cigarettes as lower risk is inaccurate. Consistent with this scenario, prior research has found participants rate low nicotine cigarettes as less harmful than other cigarettes, even when they are instructed to consider specific use assumptions when rating

product risks (e.g., Byron et al., 2018; Denlinger-Apte et al., 2017). This might be explained by other prior research on nicotine misperceptions (Bansal-Travers et al., 2010; Borrelli & Novak, 2007; Mutti et al., 2011; O'Brien et al., 2017); specifically, people may assume lower nicotine cigarettes are less harmful because these cigarettes have less nicotine, which they believe causes tobacco-related diseases. An alternative scenario is that participants rated VLN™ cigarettes as lower in health risks because they believed they would smoke VLN™ cigarettes at a lower rate or for a shorter duration than other cigarettes, thus lowering their tobacco-related disease risks; this may be accurate (see Section III). The applicant stated that this second scenario was the case, and thus did not interpret participants' ratings of VLN™ cigarettes as lower risk as inaccurate. However, the applicant provided no information to support this assertion. Additionally, the applicant did not provide any evidence regarding whether the "voluntary warning" increased or decreased perceived risk of the 18 health conditions from using the product.

The applicant's research also contained responses to open-ended questions that are relevant to understanding what participants believed about the risks of using VLN™ cigarettes; however, these responses do not clearly support one scenario or the other. These questions asked participants (1) how they would describe VLN™ cigarettes to a friend or a family member, (2) the benefits of VLN™ cigarettes, and (3) the health and addiction risks of smoking VLN™ cigarettes. While these responses provided some useful information, we note that these questions were not designed to determine the extent to which participants understood the modified risk information or the assumptions they made in rating product risks (e.g., many participants simply responded by simply noting that the products contain less nicotine than other cigarettes). Responses to these questions did not clearly support one scenario or the other, because they included a range of interpretations of the proposed claims and "voluntary warning." For example, in response to the question about how participants would describe VLN™ cigarettes to a friend, some responses reflected a generally accurate understanding of health risks, e.g.: "Health risks remains the same but 95% less nicotine." However, other responses reflected uncertainty or misunderstanding, for example:

- "Low-nicotine cigarette. Like "regular" cigarettes with reduced nicotine levels. NOT clear whether risk levels are reduced at commensurate levels."
- "It's a cigarette with 95% less nicotine so it gives you the same feeling as smoking without all of the harmful effects. Many people are addicted to the action of smoking as much as they are to the chemicals so it might be a better solution to try."

We acknowledge it is not possible to definitively determine which scenario is the case with the information provided in the application. The first scenario, which is that the lower risk ratings for VLN™ cigarettes are inaccurate, may be more likely. This is because the risk rating questions asked participants to state "what you believe is the risk of each of the following **long-term or lifetime** health-related issues," (emphasis added); this encourages participants to consider use of both products long-term. Additionally, this scenario would be consistent with literature on risk perceptions of low nicotine cigarettes that include instructions with assumptions about product use (e.g., Byron et al., 2018; Denlinger-Apte et al., 2017). This scenario is also consistent with literature on misperceptions related to nicotine's role in tobacco-related disease (Bansal-Travers et al., 2010; Borrelli & Novak, 2007; Mutti et al., 2011; O'Brien et al., 2017).

Consumer understanding of how to use VLN™ cigarettes

The applicant did not assess whether the proposed labeling and advertising would enable the public to understand how to use VLN™ cigarettes; i.e., cut down on cigarette smoking.

According to the applicant, reductions in mortality and morbidity (aside from dependence) would only be observed if smokers use VLN™ cigarettes to decrease their overall cigarette smoking. However, this information is not included in the labeling or advertising. In addition, the quantitative consumer perception study did not assess whether the proposed labeling and advertising would enable the public to understand how to use VLN™ cigarettes (i.e., to cut down on cigarette smoking). Furthermore, the applicant's qualitative research indicated confusion among some participants about how the product is intended to work (e.g., some participants commented that the labeling "Doesn't explain the link between lower nicotine content and reduction in smoking"). While the applicant did not include language encouraging product users to switch completely to the product or measure outcomes related to complete switching, it should be noted that product users who continue to smoke their usual brand of cigarettes still reduce their nicotine exposure and CPD (discussed below).

III. Is a substantial reduction in users' morbidity or mortality reasonably likely?

This section will inform the following discussion question:

- 2. Discuss the likelihood that reductions in dependence translate into substantial reductions in morbidities and mortality among individual tobacco users.*

Morbidity and mortality: Dependence as an outcome

Cigarette smokers who use VLNC cigarettes reduce their nicotine dependence.

The abuse liability of VLN™ cigarettes is significantly reduced compared to conventional cigarettes, and comparable to NRT gum. This conclusion is collectively supported by lower plasma nicotine and lower positive subjective effects ratings for VLNC cigarettes compared to usual brand, normal nicotine cigarettes in (a) the applicant's abuse liability studies, which provided actual use data in healthy adult smokers after *ad libitum* and controlled VLN™ cigarette smoking, and (b) findings from the applicant's literature review on VLNC cigarettes.

Reducing nicotine exposure can reduce nicotine dependence. There is consistent published evidence indicating that use of VLNC cigarettes for an extended duration of time is associated with significant reductions in CPD and decreased dependence scores among both smokers interested and not interested in quitting (e.g., Hatsukami et al., 2010; Walker et al., 2015; Donny et al., 2015; Hatsukami et al., 2018). Studies that evaluated CPD after 6 weeks of smoking VLNC cigarettes report reductions ranging from 11% to 46% (e.g., Donny et al., 2015; Foulds et al., 2018; Pacek et al., 2016; Tidey et al., 2017). In Hatsukami and colleagues' (2018) study, smokers who did not want to quit were assigned to a control condition (in which they continued smoking their usual brand of cigarettes) or a VLNC condition (in which they were told to immediately switch to VLNC cigarettes). The researchers found that by 20 weeks, total CPD in the VLNC cigarette condition was about half that of the control condition (see Figure 4). This between-group difference was 53% based on using a multiple imputation method for missing data and was 46% based on using a last observation carried forward method for missing data. However,

when examining within-group change, CPD decreased by about a quarter for the VLNC condition (30% based on using a multiple imputation [MI] method for missing data, 23% based on using last observation carried forward [LOCF] method for missing data) and increased by a similar amount in the control condition (30% using MI, 23% using LOCF). We note that the study was designed to make between-group comparisons and not within-group comparisons; thus, we rely more on the between-group comparison (finding the 46-53% reduction). The between-group comparison accounts for increases in smoking due to cigarettes being provided for free and therefore is more valid.

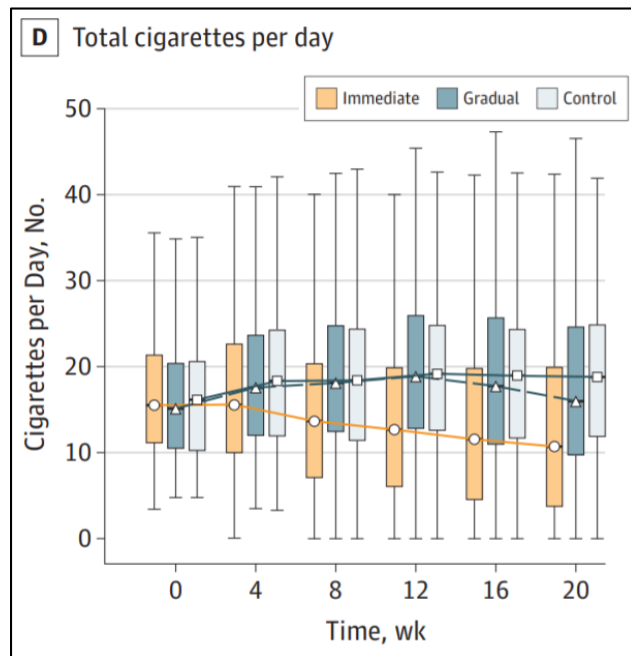


Figure 4. Among smokers not interested in quitting, changes over time in CPD between a control group (light blue) and an immediate reduction group who switched to VLNC cigarettes (yellow). For the purposes of these MRTPA reviews, we disregarded the gradual reduction group (dark blue). Source: Figure 2 in Hatsukami et al., 2018.

Previous research has also found that reducing cigarette consumption can increase the likelihood that an individual will become cigarette abstinent in the future (Hughes & Carpenter, 2006). Using VLNC cigarettes is associated with increased quit attempts in smokers not interested in quitting (Walker et al., 2015; Donny et al., 2015). Among smokers interested in quitting, switching to VLNC cigarettes may facilitate smoking abstinence as a result of reduced nicotine exposure, particularly when used in combination with NRT and behavioral intervention (Dermody et al., 2015; Hatsukami et al., 2010; Walker et al., 2012).

Thus, smoking VLN™ cigarettes can contribute to a measurable and substantial reduction in dependence resulting from reduced nicotine exposure among individual tobacco users following extended VLN™ cigarette use.

Morbidity and mortality: Other outcomes

While using the product can substantially reduce dependence, the magnitude of the reduction in other morbidities and mortality from reduced dependence remains unclear.

Studies have found that, compared to smokers who do not reduce their CPD, smokers who reduce their CPD by at least 50% decrease some, but not all, disease risks (Godtfredsen et al., 2005; Lee, 2013; Pisinger & Godtfredsen, 2007; Godtfredsen et al., 2003; Godtfredsen et al., 2002). For example, Godtfredsen and colleagues (2005) found that a reduction of at least 50% from heavy smoking (15+ CPD) was associated with a 27% reduction in lung cancer risk. While some studies (Bolliger, 2000; Bolliger et al., 2002; Eliasson et al., 2001; Hatsukami et al., 2005; Hausteine et al., 2004) found that a decrease of at least 50% CPD was associated with beneficial effects on some cardiovascular risk factors (e.g., cholesterol levels), another study found that this CPD reduction had no effect on myocardial infarction risk (Godtfredsen, 2003). Similarly, while smoking reductions of at least 50% have resulted in improvement in some pulmonary symptoms (Hatsukami et al., 2005; Stein et al., 2005), studies have not shown robust improvements in lung function (Burchfiel et al., 1995) or a reduction in the risk of hospitalization for chronic pulmonary obstructive disorder (Godtfredsen et al., 2002). Considered as a whole, the results of this research suggest that a CPD reduction of at least 50% could lead to a substantial reduction in some tobacco-related morbidities, but not others.

It is unclear what proportion of smokers who use VLNC cigarettes will reduce their CPD by at least 50%. As described above, a 20-week study found that CPD among smokers assigned to smoke VLNC cigarettes was about half that of the control; however, examining within-group changes revealed that CPD decreased by about a quarter in the VLNC cigarette condition and increased by a similar amount in the control condition (Hatsukami et al., 2018). While this CPD reduction would constitute a substantial reduction in dependence as a morbidity, the magnitude of the reduction in other morbidities from reduced dependence remains unclear.

Additionally, studies have not demonstrated that a reduction in CPD reduces mortality. A prospective cohort study of approximately 20,000 people showed no change in all-cause mortality, mortality from COPD/respiratory infections, or mortality from cardiovascular disease in heavy smokers who reduced their tobacco consumption by at least 50% compared to continued heavy smokers (Godtfredsen et al., 2002). Another study found similar results, with no change in all-cause mortality or mortality due to smoking-related cancer after smoking reduction (Tverdal & Bjartveit, 2006).

Aside from changes in CPD, the increase in quit attempts and potential increase in quit success associated with using VLNC cigarettes could lead to a decrease in morbidity and mortality.

IV. Potential impact to population health

This section will inform the following discussion questions:

3. *Discuss the extent to which the following groups are likely to try and progress to regularly using the proposed modified risk tobacco products:*
 - a. *Never smokers*
 - b. *Former smokers*

4. Discuss the extent to which the following groups will dual use the proposed modified risk products with their usual brand of cigarettes or exclusively use the proposed modified risk products:
 - a. Cigarette smokers who want to quit smoking
 - b. Cigarette smokers who do not want to quit smoking

Likelihood of use among nonsmokers, including youth and young adults

Overall, it is unlikely that nonsmokers will try this product and progress to regularly using it.

The applicant’s consumer perception studies found that nonsmokers have low intentions to use VLN™ cigarettes (Figure 5). Never and former smokers’ intentions to purchase and intentions to use VLNC cigarettes “on a regular, ongoing basis” were low, with means between 1 and 2 (on a 5-point scale for purchase, 5 = “Definitely Would Purchase”; and a 6-point scale for use, 6 = “Definitely Would Use”). Former and never smokers randomized to see Marlboro Gold cigarette packs or VLN™ cigarette packs reported higher intentions to *purchase* VLN™ cigarettes compared to Marlboro Gold cigarettes by about 0.1-0.2 (on a 5-point scale). Never smokers also had higher intentions to *use* VLN™ cigarettes “on a regular, ongoing basis” by about 0.1 on a 6-point scale. Findings were similar for never smokers aged 21-25 years.

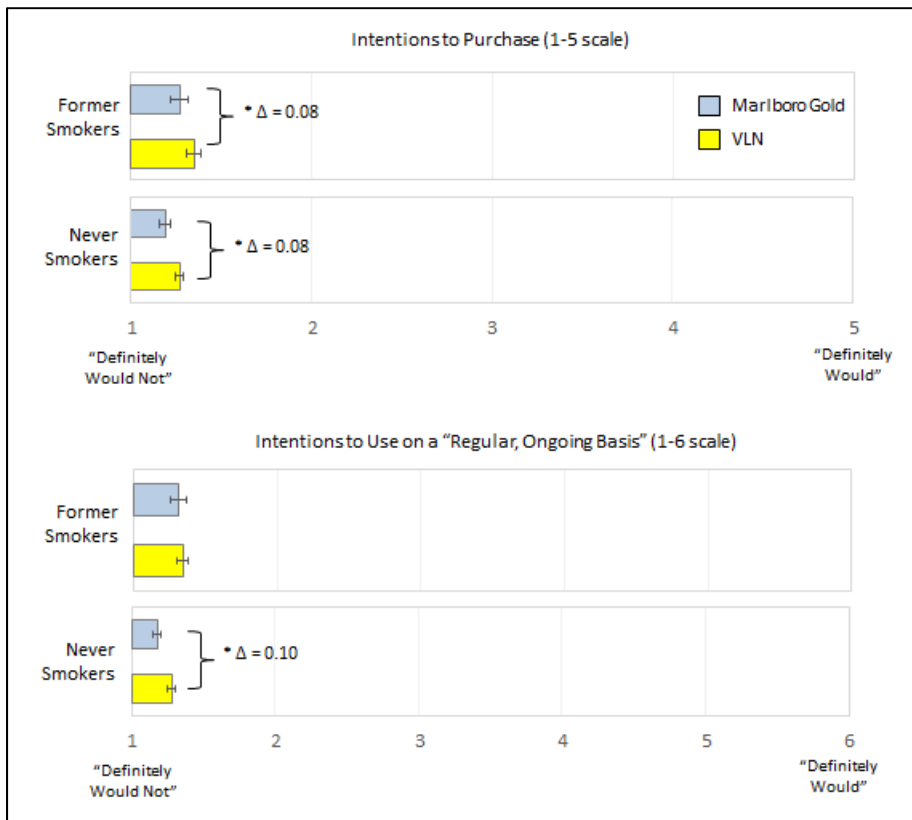


Figure 5. Former and never smokers’ intentions ratings of VLN™ and Marlboro Gold. For intentions to purchase, the study item asked, “How likely would you be to buy [VLN/Marlboro Gold]?” For intentions to use, the study item asked, “Now think about your personal intent to use [VLN/ Marlboro Gold]. By intent to use, we mean that you personally, as a non-smoker, now intend to smoke [VLN/ Marlboro Gold] on a regular, ongoing basis. Overall, what is your intent to

smoke [VLN/ Marlboro Gold] on a regular, ongoing basis?" Source: Based on data in the M/A/R/C Research Quantitative Report. Error bars: 95% CIs.

Other than noting a potential youth appeal issue with the sample of proposed advertising submitted (described in the introduction), FDA did not identify significant concerns related to youth uptake of VLN™ cigarettes. However, FDA notes that there is no direct evidence to determine whether youth nonusers would be affected the same way as adult nonusers by the proposed modified risk products. FDA is aware of one published study evaluating the impact of modified risk claims on youth (El-Touhky et al., 2018). This study found that modified risk claims similarly decrease risk perceptions among youth and adults but affected susceptibility to use the product only among adults. Given that lower risk perceptions can predict tobacco use initiation (Song et al. 2009; Strong et al. 2019), it is possible that exposing youth tobacco nonusers to the products with the proposed claims could increase their risk of initiating use of VLN™ cigarettes. However, the lower abuse liability of VLN™ cigarettes reduces the potential for youth to become addicted and to become regular smokers due to nicotine dependence.

Additionally, it may be relevant to consider that, when Quest cigarettes were on the U.S. market and advertised as “low nicotine,” “extra low nicotine,” and “nicotine free,” youth smoking rates declined (Johnston et al., 2019). Although smoking rates are affected by numerous factors, this indicates a lack of substantial increases in youth smoking rates when a similar product with similar claims was marketed. Additionally, a convenience sample of college students rated Quest cigarettes as having lower positive expectancies than Marlboro Lights on a scale that predicted willingness to try the products (O’Connor et al., 2007), suggesting that they may be less likely to initiate that product. However, the generalizability of this information is limited, because the applicant proposes to market VLN™ cigarettes using different labeling and advertising.

Likelihood of use and use patterns among smokers

Overall, current smokers have moderate to high intentions to use this product (Figure 3).

As described in Section III, over time, most cigarette smokers who continue to use this product will decrease their CPD and may increase their quit attempts (e.g., Hatsukami et al., 2018; Donny et al., 2015; Dermody et al., 2015; Hatsukami et al., 2010).

The applicant’s consumer perception study found that current cigarette smokers have moderate to high intentions to purchase and intentions to use VLN™ cigarettes “on a regular, ongoing basis” (Figure 6). Specifically, mean ratings were between 3 and 4 (on a 5-point scale for purchase, 5 = “Definitely Would Purchase”; and a 6-point scale for use, 6 = “Definitely Would Use”). Current smokers randomized to see Marlboro Gold cigarette packs or VLN™ cigarette packs reported higher intentions to use VLN™ cigarettes compared to Marlboro Gold cigarettes. These mean differences were significant and were 0.6 for smokers overall, 0.3 for smokers not intending to quit, and 0.9 for smokers intending to quit. However, actual differences in intentions to use these products may be smaller, as participants who smoke Marlboro Gold were not assigned to that condition in the study.

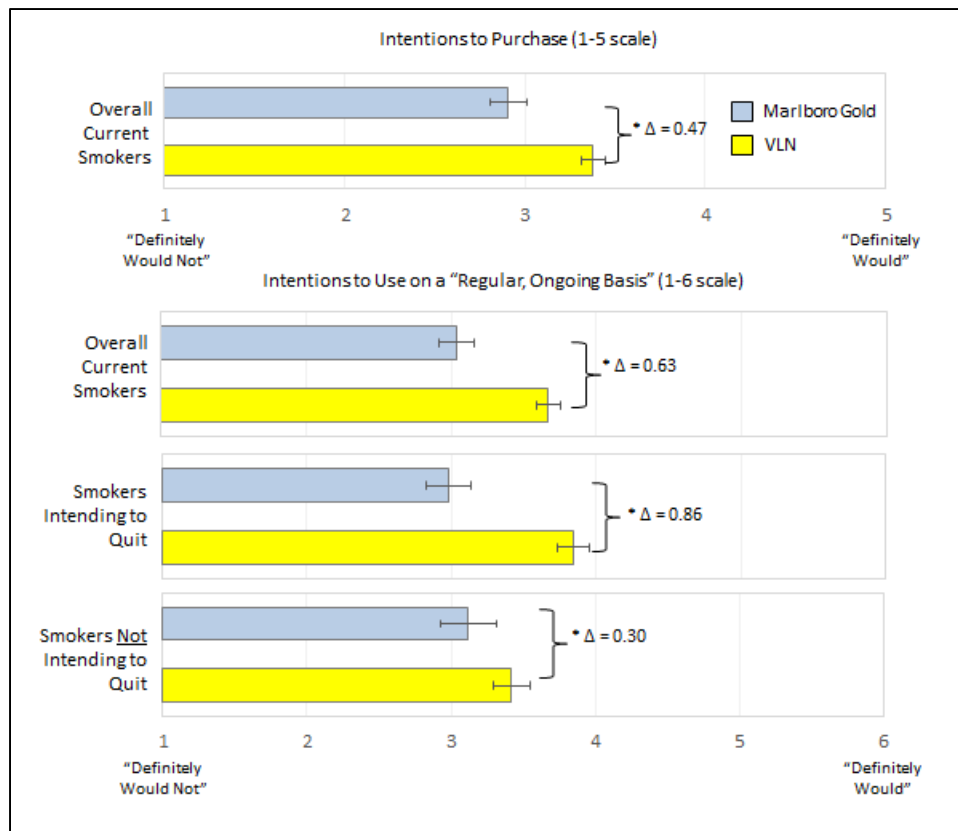


Figure 6. Current smokers' intentions ratings of VLN™ and Marlboro Gold. For intentions to purchase, the study item asked, "How likely would you be to buy [VLN/Marlboro Gold]?" For intentions to use, the study item asked, "Now think about your personal intent to use [VLN/Marlboro Gold]. By intent to use, we mean that you personally now intend to smoke [VLN/Marlboro Gold] on a regular, ongoing basis. Overall, what is your intent to smoke [VLN/Marlboro Gold] on a regular, ongoing basis?" Source: Based on data in the M/A/R/C Research Quantitative Report. Error bars: 95% CIs.

Due to the abuse liability profile, it is unlikely that current tobacco users who are not interested in quitting will find VLN™ cigarettes appealing and switch to them. However, the consumer perception study finds that regardless of interest in quitting, smokers perceive the product to be lower risk compared to other cigarettes; therefore, it is possible that smokers not interested in quitting may switch for this reason. In clinical studies, when smokers not interested in quitting primarily use this product, they still decreased their CPD and had greater quit attempts compared to those who continued smoking normal nicotine content cigarettes (e.g., Hatsukami et al., 2018; Donny et al., 2015).

Furthermore, the majority of cigarette smokers are interested in quitting in the next 6 months (e.g., Persoskie et al., 2013). Among smokers interested in quitting, switching to VLNC cigarettes may facilitate smoking abstinence as a result of reduced nicotine exposure, particularly when used in combination with NRT and behavioral intervention (Dermody et al., 2015; Hatsukami et al., 2010; Walker et al., 2012). As such, there are no concerns related to increased risk of addiction or decreased likelihood of cessation.

The available literature provides little to no evidence that VLN™ cigarettes increase risk of adverse effects (e.g., exacerbations of psychiatric symptomatology, other substance use) among the vulnerable

populations of smokers with mental illness or substance use disorders. There is no evidence that smoking VLN™ cigarettes would be associated with increased abuse liability among these smokers. The literature supports that in smokers with mental health symptoms, VLNC cigarettes were not associated with increased markers of compensatory smoking (e.g., smoking topography, carbon monoxide) compared to the general population (Higgins et al., 2017; Tidey et al., 2016). Researchers also assessed psychiatric symptomatology as a function of VLNC cigarette use and found that VLNC cigarettes were associated with improvements in mood symptoms, likely due to nicotine's anxiety-increasing properties (Tidey et al., 2017). Although rare, there have been reports of adverse events related to nicotine withdrawal in a general population sample among individuals with a history of poor mental health. For example, two subjects in Hatsukami and colleague's 2018 study were discontinued due to suicidal ideation, assessed as possibly related to VLNC cigarettes and nicotine withdrawal. Studies also found no evidence that alcohol or marijuana use moderates the effects of VLNC cigarettes (Pacek et al., 2016; Dermody et al., 2016). Overall, for smokers with mental illness or substance use disorders, VLNC cigarettes can serve as an interim transition to reduce nicotine dependence and may eventually aid in quit attempts.

Population model

The applicant's population model has limited utility but indicates that marketing the product may provide some overall benefit to population health.

The applicant's population model has limited utility because it is unclear how population model inputs derived from clinical studies will generalize to the real-world. Specifically, the population model uses inputs based on clinical studies, rather than actual use studies. These clinical studies are based on smokers who do not want to quit (which could deflate estimated benefits), and who are forced to switch and paid to participate (which could inflate estimated benefits). Additionally, the population model does not account for product uptake among nonusers, nor does it account for the effect of the modified risk claims. While the model has likely overestimated population health benefit, it indicates that marketing the product may provide some overall benefit to the population.

V. FDA preliminary conclusions

FDA is evaluating the products with the reduced exposure claims under requirements of Section 911(g)(2) of the FD&C Act. FDA's preliminary conclusions are as follows:

- Substantiation: The three proposed claims are substantiated.
- Consumer understanding: Consumers understand the addiction risk of using the products relative to normal nicotine content cigarettes, but it is unclear whether they understand the other relative health risks of using the products; they perceive the products to be lower risk than other cigarettes.
- Morbidity and mortality: The proposed modified risk products can substantially reduce dependence among individual tobacco users. The magnitude of the reduction in other morbidities and mortality from reduced dependence remains unclear.
- Population health impact: Nonsmokers have low intentions to use the products, and current smokers have moderate intentions to use the products. All smoker groups have higher intentions to purchase VLN™ cigarettes compared to Marlboro Gold cigarettes.

References

- Bansal-Travers, M., Cummings, K. M., Hyland, A., Brown, A., & Celestino, P. (2010). Educating smokers about their cigarettes and nicotine medications. *Health Education Research, 25*, 678-686.
- Borrelli, B., & Novak, S. P. (2007). Nurses' knowledge about the risk of light cigarettes and other tobacco "harm reduction" strategies. *Nicotine & Tobacco Research, 9*, 653-661.
- Bolliger, C. T. (2000). Practical experiences in smoking reduction and cessation. *Addiction, 95*, S19-S24.
- Bolliger, C. T., Zellweger, J. P., Danielsson, T., van Biljon, X., Robidou, A., Westin, Å., ... & Säwe, U. (2002). Influence of long-term smoking reduction on health risk markers and quality of life. *Nicotine & Tobacco Research, 4*, 433-439.
- Burchfiel, C. M., Marcus, E. B., Curb, J. D., MacLean, C. J., Vollmer, W. M., Johnson, L. R., ... & Buist, A. S. (1995). Effects of smoking and smoking cessation on longitudinal decline in pulmonary function. *American Journal of Respiratory and Critical Care Medicine, 151*, 1778-1785.
- Byron, M. J., Jeong, M., Abrams, D. B., & Brewer, N. T. (2018). Public misperception that very low nicotine cigarettes are less carcinogenic. *Tobacco Control, 27*, 712-714.
- Denlinger-Apte, R. L., Joel, D. L., Strasser, A. A., & Donny, E. C. (2017). Low nicotine content descriptors reduce perceived health risks and positive cigarette ratings in participants using very low nicotine content cigarettes. *Nicotine & Tobacco Research, 19*, 1149-1154.
- Denlinger, R. L., Smith, T. T., Murphy, S. E., Koopmeiners, J. S., Benowitz, N. L., Hatsukami, D. K., ... & Donny, E. C. (2016). Nicotine and anatabine exposure from very low nicotine content cigarettes. *Tobacco Regulatory Science, 2*(2), 186-203.
- Dermody, S. S., Donny, E. C., Hertsgaard, L. A., & Hatsukami, D. K. (2015). Greater reductions in nicotine exposure while smoking very low nicotine content cigarettes predict smoking cessation. *Tobacco Control, 24*, 536-539.
- Dermody, S. S., Tidey, J. W., Denlinger, R. L., Pacek, L. R., al'Absi, M., Drobles, D. J., . . . Donny, E. C. (2016). The impact of smoking very low nicotine content cigarettes on alcohol use. *Alcoholism, Clinical and Experimental Research, 40*(3), 606-615.
- Donny, E. C., Denlinger, R. L., Tidey, J. W., Koopmeiners, J. S., Benowitz, N. L., Vandrey, R. G., . . . Hatsukami, D. K. (2015). Randomized trial of reduced-nicotine standards for cigarettes. *New England Journal of Medicine, 373*, 1340-1349.
- Eliasson, B., Hjalmarson, A., Kruse, E., Landfeldt, B., & Westin, Å. (2001). Effect of smoking reduction and cessation on cardiovascular risk factors. *Nicotine & Tobacco Research, 3*, 249-255.
- El-Toukhy, S., Baig, S. A., Jeong, M., Byron, J. M., Ribisl, K. M., Brewer, N. T. (2018). Impact of tobacco product claims of lower exposure and lower risk. *Tobacco Control, 27*, s62-s69.
- Foulds, J., Hobkirk, A., Wasserman, E., Richie, J., Veldheer, S., Krebs, N. M., . . . Muscat, J. (2018). Estimation of compliance with exclusive smoking of very low nicotine content cigarettes using plasma cotinine. *Preventive Medicine, 117*, 24-29.
- Godtfredsen, N. S., Holst, C., Prescott, E., Vestbo, J., & Osler, M. (2002). Smoking reduction, smoking cessation, and mortality: a 16-year follow-up of 19,732 men and women from The Copenhagen Centre for Prospective Population Studies. *American Journal of Epidemiology, 156*, 994-1001.
- Godtfredsen, N. S., Osler, M., Vestbo, J., Andersen, I., & Prescott, E. Smoking reduction, smoking cessation, and incidence of fatal and non-fatal myocardial infarction in Denmark 1976-1998: a pooled cohort study. (2003). *Journal of Epidemiology and Community Health, 57*(6), 412-416.
- Godtfredsen, N. S., Prescott, E., & Osler, M. (2005). Effect of smoking reduction on lung cancer risk. *Journal of the American Medical Association, 294*, 1505-1510.
- Haustein, K. O., Krause, J., Haustein, H., Rasmussen, T., & Cort, N. (2004). Changes in hemorheological and biochemical parameters following short-term and long-term smoking cessation induced by

- nicotine replacement therapy (NRT). *International Journal of Clinical Pharmacology and Therapeutics*, 42(2), 83-92.
- Hatsukami, D. K., Kotlyar, M., Allen, S., Jensen, J., Li, S., Le, C., & Murphy, S. (2005). Effects of cigarette reduction on cardiovascular risk factors and subjective measures. *Chest*, 128, 2528-2537.
- Hatsukami, D. K., Kotlyar, M., Hertzgaard, L. A., Zhang, Y., Carmella, S. G., Jensen, J. A., . . . Hecht, S. S. (2010). Reduced nicotine content cigarettes: effects on toxicant exposure, dependence and cessation. *Addiction*, 105, 343-355.
- Hatsukami, D. K., Luo, X., Dick, L., Kangkum, M., Allen, S. S., Murphy, S. E., . . . al'Absi, M. (2017). Reduced nicotine content cigarettes and use of alternative nicotine products: exploratory trial. *Addiction*, 112(1), 156-167.
- Hatsukami, D. K., Luo, X., Jensen, J. A., al'Absi, M., Allen, S. S., Carmella, S. G., . . . Donny, E. C. (2018). Effect of immediate vs gradual reduction in nicotine content of cigarettes on biomarkers of smoke exposure: A randomized clinical trial. *Journal of the American Medical Association*, 320, 880-891.
- Higgins, S. T., Heil, S. H., Sigmon, S. C., Tidey, J. W., Gaalema, D. E., Hughes, J. R., . . . Tursi, L. (2017). Addiction potential of cigarettes with reduced nicotine content in populations with psychiatric disorders and other vulnerabilities to tobacco addiction. *JAMA Psychiatry*, 74(10), 1056-1064.
- Hughes, J. R., & Carpenter, M. J. (2006). Does smoking reduction increase future cessation and decrease disease risk? A qualitative review. *Nicotine & Tobacco Research*, 8(6), 739-749.
- Johnston, L. D., Miech, R. A., O'Malley, P. M., Bachman, J. G., Schulenberg, J. E., & Patrick, M. E. (2019). Monitoring the Future national survey results on drug use 1975-2018: Overview, key findings on adolescent drug use. University of Michigan - Ann Arbor: Institute for Social Research.
- Lee, P. N. (2013). The effect of reducing the number of cigarettes smoked on risk of lung cancer, COPD, cardiovascular disease and FEV1—A review. *Regulatory Toxicology and Pharmacology*, 67(3), 372-381.
- Mutti, S., Hammond, D., Borland, R., Cummings, M. K., O'Connor, R. J., & Fong, G. T. (2011). Beyond light and mild: Cigarette brand descriptors and perceptions of risk in the International Tobacco Control (ITC) Four Country Survey. *Addiction*, 106, 1166-1175.
- Nardone, N., Donny, E. C., Hatsukami, D. K., Koopmeiners, J. S., Murphy, S. E., Strasser, A. A., . . . Benowitz, N. L. (2016). Estimations and predictors of non-compliance in switchers to reduced nicotine content cigarettes. *Addiction*, 111(12), 2208-2216.
- O'Brien, E. K., Nguyen, A. B., Persoskie, A., & Hoffman, A. C. (2017). U.S. adults' addiction and harm beliefs about nicotine and low nicotine cigarettes. *Preventive Medicine*, 96, 94-100.
- O'Connor, R. J., Ashare, R. L., Fix, B. V., Hawk, L. W., Cummings, K. M., & Schmidt, W. C. (2007). College students' expectancies for light cigarettes and potential reduced exposure products. *American Journal of Health Behavior*, 31, 402-410.
- Pacek, L. R., Vandrey, R., Dermody, S. S., Denlinger-Apte, R. L., Lemieux, A., Tidey, J. W., . . . Donny, E. C. (2016). Evaluation of a reduced nicotine product standard: Moderating effects of and impact on cannabis use. *Drug and Alcohol Dependence*, 167, 228-232.
- Persoskie, A., & Nelson, W. L. (2013). Just blowing smoke? Social desirability and reporting of intentions to quit smoking. *Nicotine & Tobacco Research*, 15, 2088-2093.
- Pisinger, C., & Godtfredsen, N. S. (2007). Is there a health benefit of reduced tobacco consumption? A systematic review. *Nicotine & Tobacco Research*, 9, 631-646.
- Stein, M. D., Weinstock, M. C., Herman, D. S., & Anderson, B. J. (2005). Respiratory symptom relief related to reduction in cigarette use. *Journal of General Internal Medicine*, 20, 889-894.
- Tidey, J. W., Cassidy, R. N., & Miller, M. E. (2016). Smoking topography characteristics of very low nicotine content cigarettes, with and without nicotine replacement, in smokers with schizophrenia and controls. *Nicotine & Tobacco Research*, 18, 1807-1812.

- Tidey, J. W., Pacek, L. R., Koopmeiners, J. S., Vandrey, R., Nardone, N., Drobes, D. J., . . . Donny, E. C. (2017). Effects of 6-Week Use of Reduced-Nicotine Content Cigarettes in Smokers With and Without Elevated Depressive Symptoms. *Nicotine & Tobacco Research, 19*, 59-67.
- Tverdal, A., & Bjartveit, K. (2006). Health consequences of reduced daily cigarette consumption. *Tobacco Control, 15*, 472-480.
- Walker, N., Howe, C., Bullen, C., Grigg, M., Glover, M., McRobbie, H., . . . Whittaker, R. (2012). The combined effect of very low nicotine content cigarettes, used as an adjunct to usual Quitline care (nicotine replacement therapy and behavioural support), on smoking cessation: A randomized controlled trial. *Addiction, 107*, 1857-1867.
- Walker, N., Fraser, T., Howe, C., Laugesen, M., Truman, P., Parag, V., . . . Bullen, C. (2015). Abrupt nicotine reduction as an endgame policy: A randomised trial. *Tobacco Control, 24*, e251-257.

Appendix A: Statutory Requirements for Modified Risk Tobacco Products (MRTPs) and Overview of FDA Review Process

The Federal Food, Drug, and Cosmetic Act (FD&C Act) defines “modified risk tobacco product” (MRTP) 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 [Section 911(b)(1)]. This means any tobacco product for which:

- 1) the label, labeling, or advertising of which represents explicitly or implicitly that:
 - a) the tobacco product presents a lower risk of tobacco-related disease or is less harmful than one or more other commercially marketed tobacco products;
 - b) the tobacco product or its smoke contains a reduced level of a substance or presents a reduced exposure to a substance; or
 - c) the tobacco product or its smoke does not contain or is free of a substance;
- 2) the label, labeling, or advertising of which uses the descriptors “light”, “mild”, “low”, or similar descriptors; or
- 3) the tobacco product manufacturer has taken any action directed to consumers through the media or otherwise, other than by means of the tobacco product’s label, labeling, or advertising, after June 22, 2009, respecting the product 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 is free of, a substance or substances. [Section 911(b)(2)]

Before an MRTP can be introduced into interstate commerce, an order from FDA under Section 911(g) must be issued and in effect with respect to the product. If the proposed modified risk tobacco product is also a new tobacco product, it must comply with the premarket review requirements under section 910(a)(2).

To request a Section 911(g) order from FDA, an applicant must file a modified risk tobacco product application (MRTPA) under Section 911(d). The MRTPA should include, among other things, information about the various aspects of the tobacco product as well as information to enable FDA to assess the impacts of marketing the proposed MRTP on individual health outcomes and population-level outcomes. Examples of population outcomes include initiation and cessation of tobacco product use. In March 2012, FDA published a draft guidance for public comment, entitled “Modified Risk Tobacco Product Applications,” which discusses the submission of applications for an MRTP under Section 911 of the FD&C Act and considerations regarding studies and analyses to include in an MRTPA (<https://www.congress.gov/111/plaws/publ31/PLAW-111publ31.pdf>). When finalized, this guidance will represent the Agency’s current thinking on the topic.

Section 911(g) of the FD&C Act describes what applicants must demonstrate in order to receive a modified risk order. There are two types of orders that can be issued under Sections 911(g)(1) and (2) of the FD&C Act.

Risk Modification Order: FDA shall issue an order under Section 911(g)(1) of the FD&C Act (risk modification order) only if it determines the applicant has demonstrated that the product, as it is actually used by consumers, will:

- Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and
- 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.

If FDA issues a marketing authorization order under this statute, FDA may require that the product comply with requirements relating to advertising and promotion of the tobacco product (Section 911(h)(5) of the FD&C Act).

Exposure Modification Order: Alternatively, for products that cannot receive a risk modification order from FDA under Section 911(g)(1) of the FD&C Act, FDA may issue an order under Section 911(g)(2) of the FD&C Act (exposure modification order). The maximum duration of an exposure modification order under the statute is 5 years. Under Section 911(g)(2) of the statute, FDA may issue an order if it determines that the applicant has demonstrated that:

- Scientific evidence is not available and, using the best available scientific methods, cannot be made available without conducting long-term epidemiological studies for an application to meet the standards for a risk modification order under Section 911(g)(1);
- Such an order would be appropriate to promote the public health;
- Any aspect of the label, labeling, and advertising for the product that would cause the product to be a modified risk tobacco product is limited to an explicit or implicit representation that the tobacco product or its smoke does not contain or is free of a substance or contains a reduced level of a substance, or presents a reduced exposure to a substance in tobacco smoke;
- The 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;
- The magnitude of overall reductions in exposure to the substance(s) which are the subject of the application is substantial, such substance or substances are harmful, and the product, as actually used, exposes consumers to the specified reduced level of the substance(s);
- The product, as actually used by consumers, will not expose them to higher levels of other harmful substances compared to similar types of tobacco products on the market, unless such increases are minimal and the reasonably likely overall impact of product use remains a substantial and measurable reduction in overall morbidity and mortality among individual tobacco users;
- 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 is or has been demonstrated to be less harmful; or presents or has been demonstrated to present less of a risk of disease than one or more other commercially-marketed tobacco products; and
- Issuance of the exposure modification 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.

In evaluating the benefit to health of individuals and of the population as a whole under both Sections 911(g)(1) and (g)(2) of the FD&C Act, FDA must take into account:

- The relative health risks the MRTP presents to individuals;
- The increased or decreased likelihood that existing tobacco product users, who would otherwise stop using such products, will switch to using the MRTP;
- The increased or decreased likelihood that persons who do not use tobacco products will start using the MRTP;
- The risks and benefits to persons from the use of the MRTP compared to the use of smoking cessation drug or device products approved by FDA to treat nicotine dependence; and
- Comments, data, and information submitted to FDA by interested persons.

Once an MRTPA is submitted, FDA performs preliminary administrative reviews to determine whether to accept and file it. In general, after filing an application, FDA begins substantive scientific review. As part of this scientific review, FDA will seek and consider public comments on the application, as well as recommendations from the FDA Tobacco Products Scientific Advisory Committee (TPSAC). FDA intends to review and act on a complete MRTPA within 360 days of FDA filing an application. An order authorizing an MRTP refers to a specific product, not an entire class of tobacco products (e.g., all smokeless products).

An FDA order authorizing an MRTP is not permanent; it is for a fixed period of time that will be determined by FDA and specified in the order. To continue to market an MRTP after the set term, an applicant would need to seek renewal of the order and FDA would need to determine that the findings continue to be satisfied. Also, if at any time FDA determines that it can no longer make the determinations required for an MRTP order, FDA is required to withdraw the order. Before FDA withdraws an MRTP order, it will provide an opportunity for an informal hearing as required under the law.

