U.S. FOOD & DRUG ADMINISTRATION

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Scientific Review of Modified Risk Tobacco Product Application (MRTPA) Under Section 911 (d) of the FD&C Act – Technical Project Lead

SUBMISSION INFORMATION			
Applicant	22nd Century Group Inc.		
Product Manufacturer	NASCO Products, LLC		
Submission Date	May 17, 2019	**FDA Receipt Date**	May 20, 2019
Purpose	☐ Risk Modification (911(g)(1) order ☒ Exposure Modification (911(g)(2) order		
Claims	• Claim #1: "95% less nicotine" • Claim #2: "Helps reduce your nicotine consumption" • Claim #3: "...greatly reduces your nicotine consumption."		

PROPOSED MODIFIED RISK TOBACCO PRODUCTs	
MR0000159: VLN™ King	
Product Category	Cigarettes
Product Sub-Category	Combusted, Filtered
Package Type	Hard Pack
Package Quantity	20 Cigarettes
Characterizing Flavor	None
Length	83 mm
Diameter	7.9 mm
Ventilation	13 %
MR0000160: VLN™ Menthol King	
Product Category	Cigarettes
Product Sub-Category	Combusted, Filtered
Package Type	Hard Pack
Package Quantity	20 Cigarettes
Characterizing Flavor	Menthol
Length	83 mm
Diameter	7.9 mm
Ventilation	13 %

Cross-referenced Submission(s)	Cross-referenced STN	Primary STN(s)
	(b) (4)	APPLIES TO ALL STNs ABOVE

DISCIPLINES REVIEWED	DATE OF REVIEW
Engineering	December 15, 2021
Chemistry	December 16, 2021
Toxicology	December 16, 2021
Social Science	December 16, 2021
Behavioral Clinical Pharmacology	December 16, 2021
Medical	December 17, 2021
Epidemiology	December 16, 2021
Environmental Science	December 15, 2021
OCE Review (DEM)	December 17, 2021

Recommended Action(s)

☒ Issue a Modified Risk Grant letter
☐ Issue a Denial letter

Technical Project Lead (TPL):

/S/

Cindy Tworek, Ph.D., M.P.H.
Chief, Social Science
Division of Population Health Science

Signatory Decision:

☒ Concur with TPL recommendation and basis of recommendation

☐ Concur with TPL recommendation with additional comments (see separate memo)

☐ Do not concur with TPL recommendation (see separate memo)

/S/

Matthew R. Holman, Ph.D.
Director
Office of Science

Table of Contents

I. Executive Summary

A. Background

On May 17, 2019, 22nd Century Group Inc. submitted modified risk tobacco product applications (MRTPAs) stating that it 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, which were received by FDA on May 20, 2019.

Under section 910 of the FD&C Act, the applicant submitted premarket tobacco product applications (PMTAs) and requested authorization of the same products that are the subject of these MRTPAs, named Moonlight and Moonlight Menthol[1] combustible cigarettes, without modified risk claims. FDA authorized the marketing of the Moonlight and Moonlight Menthol combusted cigarettes without modified risk claims on December 17, 2019. The technical project lead (TPL) review for the accompanying PMTAs provides detail on the engineering, chemistry, stability, and manufacturing of the products, including the results of FDA inspections of manufacturing sites.[2] Where relevant, the present review reflects determinations made in the PMTA TPL review.

This review addresses the exposure modification pathway under section 911(g)(2) of the FD&C Act. The focus of this review of the MRTPAs is on evaluating: (1) the relative health risks of the proposed modified risk tobacco products (MRTPs) compared to combusted cigarettes to individual tobacco users; (2) consumer understanding and perception of VLN™ cigarettes marketed with the proposed claims; and (3) population health impact, including population health impact on tobacco users, tobacco users' and nonusers' likelihood of using the product after exposure to the proposed modified risk claims, and the applicant's population health model.

B. Exposure Modification Order Request

The applicant has requested an exposure modification order under section 911(g)(2) of the FD&C Act to market these products with the following claims:

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

Additionally, FDA identified the following claims in the advertising that was submitted by the applicant:

[1] On October 2, 2019, the applicant submitted an amendment to its PMTAs, notifying FDA the company was changing the product names from VLN™ King and VLN™ Menthol to Moonlight and Moonlight Menthol, respectively.
[2] The PMTA TPL reviews are available at: https://www.fda.gov/tobacco-products/premarket-tobacco-product-applications/premarket-tobacco-product-marketing-orders

- Claim #4: “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 0.27 mg of nicotine.”

- Claim #5: “Without exception, VLN™ cigarettes contain at least 95% less nicotine than the top 100 cigarette brands in the United States.”

- Claim #6: “22nd Century’s VLN™ cigarettes contain an average of 0.27 mg nicotine - -at least 95% less nicotine compared to conventional cigarettes.”

- Claim #7: “22nd Century’s VLN™ cigarettes feature the same nicotine content as the lowest nicotine style of the Company’s SPECTRUM research cigarettes.”

- Claim #8: “VLN™ cigarettes contain 0.27 ± 0.1 mg nicotine.”

- Claim #9: “As a result of our unique technology and plant breeding expertise, VLN™ tobacco grows with 95% less nicotine than conventional tobacco.”

- Claim #10: Several examples utilize a graph depicting nicotine levels of VLN™ cigarettes compared to several other cigarette brands.

Claims #1-3 appear on the submitted product labels, labeling, and advertising (LLA). Claims #4-10 appear only in the submitted product advertising. The labels and most of the advertising also include the following information, described by the applicant as a disclaimer[3]: “Nicotine is addictive. Less nicotine does NOT mean safer. All cigarettes can cause disease and death.”

We also note that both products include VLN™ in their name, which stands for ‘very low nicotine’. FDA has reviewed this language and finds it to be substantiated as descriptive for the amount of nicotine related to the product contents. Since the ‘low’ amount of nicotine contained in these products has been substantiated, we find that VLN™ is an accurate description for the product nicotine content and do not have concerns with it.

Under section 911(g)(2) of the FD&C Act, exposure modification orders may be granted by FDA when the available evidence is not sufficient for a risk modification order under section 911(g)(1). Specifically, FDA may issue an exposure modification order under section 911(g)(2) (the "special rule") if it determines that the applicant has demonstrated that:

- 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

[3] The applicant refers to the statement, “Nicotine is addictive. Less nicotine does NOT mean safer. All cigarettes can cause disease and death.” variously as a “disclaimer” (Section V “Labels, Labeling, and Advertising,” p. 3; Section VII “Summary of All Research Findings,” p. 72) and “voluntary warning” (Section V “VLN™ Cigarettes: Labels, Labeling, and Advertising,” pp. 2, 8-9). In this review, the word “disclaimer” refers to the applicant’s use of this term and does not reflect FDA’s independent conclusion regarding characterization of the information.

substance or contains a reduced level of a substance, or presents a reduced exposure to a substance in tobacco smoke;

- 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 obtaining an order under section 911(g)(1); and

- The scientific evidence that is available without conducting long-term epidemiological studies demonstrates that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies (section 911(g)(2)(A) of the FD&C Act).

Furthermore, for FDA to issue an exposure modification order, FDA must find that the applicant has demonstrated that:

- The magnitude of overall reductions in exposure to the substance or substances that 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 or substances;

- The product as actually used by consumers will not expose them to higher levels of other harmful substances compared to the similar types of tobacco products then on the market unless such increases are minimal and the reasonably likely overall impact of use of the product 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 (section 911(g)(2)(B) of the FD&C Act).

In making the determinations under section 911(g)(2) of the FD&C Act, FDA must take into account:

- The relative health risks to individuals of the modified risk tobacco product;

- The increased or decreased likelihood that existing tobacco product users who would otherwise stop using such products will switch to using the modified risk tobacco product;

- The increased or decreased likelihood that persons who do not use tobacco products will start using the modified risk tobacco product;

- The risks and benefits to persons from the use of the modified risk tobacco product 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 (section 911(g)(4) of the FD&C Act).

Unlike the section 911(g)(1) standard, which requires scientific evidence showing actual risk reduction (e.g., a finding that the product, as actually used by consumers, *will significantly reduce* harm and risk to individual users; a finding that the product, as actually used by consumers, *will benefit* the health of the population a as whole), section 911(g)(2) establishes a lower standard, which allows FDA to issue an order when risk reduction has not yet been demonstrated but is reasonably likely based on demonstrated reductions in exposure (e.g., a finding that a reduction in morbidity or mortality among individual users is *reasonably likely* in subsequent studies; a finding that issuance of an order is *expected* to benefit the health of the population as a whole).

Furthermore, FDA must ensure that the advertising and labeling of the MRTP enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation to all tobacco-related diseases and health conditions (section 911(h)(1) of the FD&C Act).

To the extent possible, the assessment integrates the various threads of evidence regarding the product and its potential effects on health and tobacco use behavior, including tobacco use initiation, to determine both the net effect of the product on overall tobacco-related morbidity and mortality and the distribution of the benefits and harms across the population. This determination also considers these product applications in the context of the current marketplace where menthol cigarette products are legally sold to consumers.[4] In particular, the recommendation considers that VLN™ Menthol King provides an opportunity for menthol smokers to reduce their nicotine consumption and reduce their exposure to nicotine, potentially decreasing their cigarettes per day smoked.

C. Summary of findings

After conducting a thorough scientific review of: the information contained in the MRTPAs; the recommendations from the Tobacco Products Scientific Advisory Committee (TPSAC); comments, data, and information submitted to FDA by interested persons; and other scientific information identified by the agency from other sources, I conclude that:

- With respect to the exposure modification order request, the applicant **has demonstrated** that the products sold or distributed with the proposed modified risk information meet the standard under section 911(g)(2) of the FD&C Act, including that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies, and issuance of an order is expected to benefit the health of

[4] In April 2021, FDA announced that it is working toward issuing a proposed product standard to prohibit menthol as a characterizing flavor in cigarettes. If a final rule banning menthol in cigarettes is issued, FDA will consider the impact of such action on the finding that VLN™ Menthol King meets the 911(g)(2) standard.

the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products. Currently, "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 set forth ..." in 911(g)(1) because issuance of an order under 911(g)(1) requires a demonstration that the product as 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". The applicant did not make such a demonstration for these products. There are outstanding questions about the manner in which consumers will use VLN, and if individual tobacco users use VLN cigarettes in the same frequency and manner as conventional cigarettes, they will not significantly reduce harm and their risk of tobacco-related disease. However, as described in this review, cigarette smokers' use of VLN cigarettes is likely to lead to reduced nicotine consumption, indicators of nicotine dependence, and likely overall cigarette consumption, which reasonably likely lead to reduced morbidity or mortality among these users, compared with continuing to smoke conventional cigarettes.

Bridging from SPECTRUM NRC102/103

Much of the evidence reviewed in these MRTPAs is based on studies of SPECTRUM NRC102 (non-menthol) and NRC103 (menthol) very low nicotine cigarettes (VLNCs). The applicant stated SPECTRUM NRC102 is the same as VLN™ King, and SPECTRUM NRC103 is the same as VLN™ Menthol King. FDA found that the cigarette weight, cigarette length, cigarette diameter, and tipping paper permeability are the same between SPECTRUM and VLN™ cigarettes. SPECTRUM cigarettes and VLN™ cigarettes also share many identical components and materials including tobacco type, tobacco blend, cigarette paper, filter, seam adhesive, and tipping adhesive. The only material difference is that the SPECTRUM tipping paper has a silver line and the name SPECTRUM printed on it, whereas the VLN™ tipping paper does not have any markings. The base tipping paper for both SPECTRUM and VLN™ cigarettes has the same porosity of (b) (4) CU and is produced by the same manufacturer. Thus, FDA finds it appropriate to bridge data from studies of SPECTRUM NRC102/103 (referred to as "VLNCs") to the proposed MRTPs. In this review, the terms VLNC cigarettes and SPECTRUM NRC102/103 are used interchangeably.

Reduced exposure claim substantiation

After thoroughly examining the modified risk LLA, I find that, consistent with section 911(g)(2)(A)(ii), any aspect of the LLA that would cause VLN™ to be a modified risk tobacco product is limited to explicit and implicit representations that VLN™ (1) contains a reduced level of nicotine and (2) presents a reduced exposure to nicotine, compared to other cigarettes. This includes the applicant-submitted claims #1-3 and the FDA-identified claims #4-10.

Eight claims discussed the nicotine content (i.e., reduced level of a substance) of the proposed MRTPs:

- Claim #1: "95% less nicotine"

- Claim #4: “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 0.27 mg of nicotine.”

- Claim #5: “Without exception, VLN™ cigarettes contain at least 95% less nicotine than the top 100 cigarette brands in the United States.”

- Claim #6: “22nd Century’s VLN™ cigarettes contain an average of 0.27 mg nicotine - -at least 95% less nicotine compared to conventional cigarettes.”

- Claim #7: “22nd Century’s VLN™ cigarettes feature the same nicotine content as the lowest nicotine style of the Company’s SPECTRUM research cigarettes.”

- Claim #8: “VLN™ cigarettes contain 0.27 ± 0.1 mg nicotine.”

- Claim #9: “As a result of our unique technology and plant breeding expertise, VLN™ tobacco grows with 95% less nicotine than conventional tobacco.”

- Claim #10: Several examples utilize a graph depicting nicotine levels of VLN™ cigarettes compared to several other cigarette brands.

Two claims discussed how the proposed MRTPs affect the users’ consumption of nicotine (i.e., reduced exposure to a substance):

- Claim #2: “Helps reduce your nicotine consumption”

- Claim #3: “...greatly reduces your nicotine consumption.”

Here, I summarize the evidence supporting the substantiation of each claim, grouped by topic area. First, I discuss claims related to nicotine content (Claims #1 and #4-10), and then I discuss claims related to reduction in nicotine consumption (Claims #2 and #3). After conducting a thorough assessment of the scientific evidence, I find that all exposure modification claims are substantiated by the evidence.

Several lines of evidence substantiate the claims related to nicotine content (Claims #1 and #4-10). First, the chemistry review found that the applicant provided a survey of 100 top-selling cigarette brands that represent 87% of all cigarettes sold in the U.S. through convenience stores in 2017. These 100 cigarettes contain a reported average of 19.4 mg nicotine per gram of tobacco on a dry weight basis (DWB) and a reported average of 12.0 mg nicotine per cigarette. The applicant reported that the tobacco nicotine content of all 10 batches of the two new VLN™ cigarettes met the applicant’s maximum nicotine specification of (b) (4) mg/g (DWB). Accordingly, the reported nicotine contents of the VLN™ cigarettes are 98% lower than the average reported nicotine contents of the top 100 cigarette brands determined both per gram of tobacco and per cigarette. In addition, both applicant-contracted and FDA nicotine test results found that nicotine levels in tobacco and mainstream smoke of VLN™ cigarettes are at least 96% lower than the majority of marketed and market-leading conventional cigarette brands.

Furthermore, batch analysis of eight batches of VLN™ cigarettes shows a slightly higher nicotine content than the 0.27 mg/cig reported by the applicant. The measured average VLN™ cigarette nicotine content was 0.29 mg/cig. However, this is within the advertised nicotine content lower and upper limit of 0.27 ±

0.10 mg/cig (0.17 and 0.37 mg/cig lower and upper limit). Based on this evidence, Claims #1, 4, 5, 6, and 8 are supported. Finally, the chemistry review notes that the two VLN™ cigarette products contain only Vector 21-41 Burley tobacco, which is a unique tobacco variety not present in any commercially-marketed cigarette tobacco. This tobacco type is genetically engineered using the applicant's proprietary technology to block several genes, which results in suppression of nicotine biosynthesis. This tobacco is also the filler in SPECTRUM research cigarettes NRC102 and mentholated NRC103. SPECTRUM NRC102 and NRC 103 also have less than (b) (4) mg/g of nicotine on a DWB, and thus has at least 95% less nicotine than the reported nicotine content for conventional cigarette tobacco. Thus, Claims #7 and 9 are supported.

Claims #1, 5, 6, and 9 all include the phrase "95% less nicotine." All but one of these claims—Claim #1—indicates the product *contains* 95% less nicotine. Claim 1 does not use the word "contains" and could therefore be referring to nicotine exposure after using the product. Accordingly, the behavioral and clinical pharmacology (BCP) review evaluated the substantiation of this meaning. The applicant's abuse liability studies, which contained actual use data in healthy adult smokers after *ad libitum* and controlled VLN™ cigarette smoking, indicate that exclusively smoking VLN™ cigarettes results in an approximate 97% reduction in plasma nicotine levels compared to smoking usual brand (UB) normal nicotine content (NNC) cigarettes. Findings from the applicant's submitted literature review on biomarkers of exposure (BOE) support these data, noting that smokers who primarily smoke or switch completely to smoking VLNC cigarettes (i.e., reduced nicotine content cigarettes that are identical or similar in nicotine content to VLN™ cigarettes) have reduced exposure to nicotine compared to smoking usual brand (UB) NNC cigarettes. The literature finds that exclusively smoking VLNC cigarettes across five days results in an average 94% reduction in urinary total nicotine equivalents (TNE). As such, by exclusively smoking VLNC cigarettes, consumers could reduce their exposure to nicotine by approximately 95%. As a result, I find this claim substantiated.

Regarding the claims about reduced nicotine consumption (Claims #2 and #3), I find that both of these claims are substantiated, including by evidence discussed in the BCP review. First, to the extent that the claims refer to a reduction of nicotine consumption resulting from complete switching and exclusive use of VLN cigarettes over UB-NNC cigarettes (i.e., with or without a concomitant reduction in overall CPD), the claims are clearly substantiated based on the greatly reduced nicotine content of VLN over UB-NNC on a per-stick basis. Furthermore, given the 95% reduced nicotine content in VLN™ cigarettes, data support that menthol and non-menthol smokers who primarily smoke VLN™ cigarettes and occasionally dual use, with other tobacco or nicotine-containing products, still experience the benefit of substantially reducing their overall exposure to nicotine compared to exclusively smoking UB-NNC cigarettes. When considering the range of non-compliance across the sample of participants assigned to smoke VLNC cigarettes (i.e., the number of UB cigarettes smoked during the course of the study in addition to VLN™ cigarettes), studies in the literature report an average 59-60% reduction in nicotine exposure over 6 to 20 weeks of VLNC cigarette use. In addition, the applicant's 6-week longitudinal study supports that, as a result of substantially reducing nicotine exposure, switching to VLNC cigarettes can lead to smoking fewer overall cigarettes per day (CPD) compared to ongoing UB-NNC cigarette smoking. These findings are supported by several VLNC cigarette studies in the published literature, including a 20-week study of VLNC cigarette use among smokers, which is the longest study of VLNC cigarettes to date (Hatsukami et al., 2018). On average, smokers assigned to switch to VLNCs had half the CPD compared to those in the UB-NNC control group. The extent of cigarette reduction depends on the extent of switching to smoking VLN™ cigarettes, although smokers who occasionally smoke UB-NNC cigarettes still experience a significant reduction in CPD compared to smoking UB-NNC cigarettes exclusively. Studies support that as

the duration of smoking VLNC cigarettes increases, the reduction in CPD increases. Thus, the available evidence supports the scientific substantiation of Claims #2 and #3.

Relatedly, consistent with section 911(g)(2)(A)(i), I find that the magnitude of the overall reduction in exposure to nicotine in VLN™ is substantial, and VLN™ as actually used exposes consumers to the specified reduced level of nicotine (i.e., "95% less nicotine" in claim 1, "helps reduce" in claim 2, and "greatly reduced" in claim 3). Also, I find that nicotine is harmful. It is addictive and is a reproductive or developmental toxicant (RDT) in FDA's established list of harmful and potentially harmful constituents.

Individual health impact among tobacco users

I find that while the proposed MRTPs may expose some smokers to higher levels of harmful and potentially harmful constituents (HPHCs), such increases are minimal; the reasonably likely overall impact of use remains a substantial reduction in morbidity among tobacco users, consistent with 911(g)(2)(B)(ii). This is based on HPHC and BOE study data comparing the proposed MRTPs to conventional cigarettes on a per-stick basis; this approach is conservative since clinical studies find that people who smoke VLNCs decrease their CPD. Comparing HPHC yields on a per cigarette basis[5] indicates that while the VLN™ products have higher levels of some HPHCs (acetaldehyde, ammonia, 4-aminobiphenol, and acrylonitrile), they have lower levels of others (e.g., NNN, acrolein, formaldehyde, benzo[a]pyrene). Toxicology reviewers concluded that although there may be higher exposures to specific constituents, these higher levels do not appear to impact the overall relative product risks and hazards, given that other constituents associated with similar adverse health outcomes are lower in the VLN™ products compared to conventional cigarettes. The overall health risks and hazards of VLN™ cigarettes compared to conventional cigarettes are likely similar if smokers of VLN™ cigarettes smoke with the same frequency as conventional cigarettes or lower if smokers of VLN™ cigarettes significantly decrease their CPD. These findings are generally consistent with evaluations of BOE in the applicant's 6-week clinical study and Hatsukami et al.'s 2018 study: among smokers assigned to use VLNC or VLN™ cigarettes, there were significant reductions in nicotine levels and in some other HPHCs. These findings provide evidence that the products will not expose consumers to high levels of non-nicotine HPHCs compared to other conventional cigarettes. Additionally, this provides some support that reductions in exposure are reasonably likely to result in a measurable and substantial reduction in morbidity or mortality among individual tobacco users; additional evidence for this is discussed next.

Consistent with section 911(g)(2)(A)(iv), I find that use of the proposed MRTPs is reasonably likely to translate to lower risk of tobacco-related morbidity and mortality among individual tobacco users in subsequent studies. The abuse liability of VLN™ cigarettes is low based on low plasma nicotine levels after using them and low subjective effects ratings. Because smokers assigned to use these products in the longest clinical study (20 weeks, Hatsukami et al., 2018) had a CPD that was 50% that of smokers assigned to smoke UB-NNC cigarettes and using the proposed MRTPs have lower dependence scores, I find it is reasonably likely that using this product reduces nicotine dependence. Nicotine dependence is a morbidity of tobacco use. Overall, reducing nicotine exposure can reduce nicotine dependence. This effect is anticipated to lead to long-term reductions in exposure to the smoking-related toxicants associated with morbidity and mortality through reducing smoking and increasing the potential for

[5] Toxicology assumes equal product use (same number of cigarettes per day (CPD), same puffing characteristics, etc.) between the VLN™ cigarettes and the comparison products.

cessation. Additionally, published epidemiological studies assessing the relationship between smoking reduction and disease risks suggested a potential benefit for some health endpoints, such as lung cancer risk, among those who reduced CPD by more than 50% compared to non-reducers. Past studies have not consistently demonstrated that a reduction in CPD reduces mortality; however, a recent study evaluating changes in smoking patterns over a longer period of time than previous studies found that all-cause mortality was lower among smokers who reduced their CPD compared to those who maintained their CPD, with greater reductions in CPD yielding greater benefits (Inoue-Choi et al., 2019). The totality of evidence presented suggests that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies. This determination predominantly stems from: (1) the 95% reduction in nicotine exposure with exclusive use of VLN™ cigarettes and at least about 50% reduction in nicotine exposure with dual use with NNC cigarettes; (2) the reduced abuse liability of VLN™ cigarettes and reduced nicotine dependence among users; (3) the substantial reduction in CPD among smokers who predominantly use VLN™ cigarettes (an estimated 50% reduction); and (4) the reduction in some tobacco morbidities (e.g., lung cancer) associated with at least a 50% reduction in CPD. The evidence also supports a finding under 911(g)(2)(A)(ii) that the LLA is limited to exposure claims; and a finding under 911(g)(2)(B)(i) that "the magnitude of the overall reductions in exposure to the substance or substances 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 or substances." *Consumer understanding*

In terms of consumer understanding, it is the TPL's view that the applications support the findings required for authorization with the inclusion of the statement "Helps you smoke less" in the LLA. The social science review evaluated consumer understanding by assessing: (1) whether consumers comprehend the explicit meaning of the proposed modified risk information, as well as whether they understand (2) VLN™ cigarettes' conditions of use, (3) addiction risk, and (4) health risks aside from addiction. Regarding (1), the social science review found that the claims are relatively simple and concrete (including the statement of "95% less"), and that each instance of LLA includes multiple statements reinforcing the main idea of substantially reduced nicotine. The applicant's qualitative research examined consumer comprehension of the proposed claims and found support for using the "95% less" wording because it was brief and made clear that the reduction in nicotine was substantial. In the applicant's quantitative research, most participants spontaneously brought up the low nicotine content when asked for an open-ended response about how they would describe the product to a friend or family member. Previously published research testing consumer comprehension of various reduced nicotine claims found that the inclusion of a percentage reduction (i.e., 95%) helped participants grasp the extent of the nicotine reduction (Byron, Hall, King, Ribisl, & Brewer, 2019). Dual-using the proposed MRTPs with other tobacco and nicotine-containing products results in a lesser nicotine exposure reduction (48-58% in the applicant's study, 59-60% in the literature). It is reasonable to expect that consumers will interpret the claim "95% less nicotine" as referring to the content of the cigarettes or the exposure they will receive if they use these cigarettes in place of conventional cigarettes rather than dual use. The alternative interpretation would require consumers to believe that somehow use of the proposed MRTPs will block their exposure to nicotine from other sources, which is unlikely. Taken together, our findings suggest that the proposed LLA would indeed enable most consumers to comprehend the claims' explicit meaning that VLN™ cigarettes contain much lower levels of nicotine than other cigarettes.

Regarding consumer understanding of (2) conditions of use, the social science review examined whether consumers would understand that VLN™ cigarettes can help smokers reduce their smoking frequency or

duration, which can reduce their exposure to nicotine and other HPHCs and potentially their disease risk. The social science review found that the proposed LLA include no information on conditions of use, such as how consumers should use VLN™ to reduce their exposure to HPHCs and potential disease risk. In qualitative in-depth interviews, some participants did not appear to understand the conditions of use: after viewing VLN™ cigarette packs with the proposed modified risk labeling, they did not understand the need to cut down or stop smoking in order to benefit from VLN™ cigarettes. In contrast, participants appeared to understand this better after viewing different packs that included the proposed claims plus an additional statement, "Helps you smoke less." Given these findings, I recommend that the order require that VLN™ cigarette LLA include "Helps you smoke less," if the LLA include one or more of the authorized exposure claims, as this statement is necessary to enable consumers to understand the manner in which they must use the product in order to obtain a benefit.

Regarding consumer understanding of (3) addiction risk, the social science review examined whether consumers would understand that VLN™ cigarettes are less addictive than other cigarettes and similarly addictive as nicotine replacement therapies (NRT). In the applicant's quantitative research, results found that this was the case: participants who viewed the proposed modified risk labeling perceived VLN™ cigarettes as substantially less addictive than other cigarettes but still perceived some risk of addiction (on a 5-point scale), placing them in a similar range as they placed NRT. This finding was also observed among participants who viewed VLN™ cigarette packs with the additional statement "Helps you smoke less." The above findings held across adult current, former, and never smokers and are consistent with prior research finding that most U.S. adults believe that nicotine is the main addictive substance in tobacco (O'Brien et al., 2017). These findings indicate that the proposed LLA enable consumers to understand VLN™ cigarettes' addiction risk.

Finally, regarding consumer understanding of (4) health risks aside from addiction, social science reviewers examined whether consumers' understanding is in line with the reasonably likely risks of the product. Specifically, social science reviewers examined whether consumers would understand that VLN™ cigarettes (a) pose moderate to high health risks, (b) are more harmful to health than NRT, (c) are reasonably likely to pose reduced disease risks (compared to other cigarettes) if consumers use them to smoke fewer cigarettes over time, and (d) are just as toxic as other cigarettes and would pose the same disease risks as other cigarettes if they are smoked in the same way (i.e., with the same frequency and duration). Importantly, findings from the applicant's research supported (a) and (b); participants indeed perceived VLN™ cigarettes as presenting risks of tobacco-related diseases that were moderate to high and significantly higher than the risks posed by NRT. Regarding (c) and (d), prior published research suggests that, without corrective or clarifying information, many U.S. consumers are at risk of misinterpreting statements about reduced nicotine content cigarettes (e.g., "Imagine if tobacco companies were required to remove 95% of the nicotine from cigarettes") to mean that the cigarettes would be less toxic and carcinogenic than other cigarettes on a per-cigarette basis (Byron et al., 2019; Bansal-Travers et al., 2010; Borrelli & Novak, 2007; Byron et al., 2018; Denlinger-Apte et al., 2017; Mutti et al., 2011; O'Brien et al., 2017). Indeed, the applicant's quantitative research found that, after viewing VLN™ packs with the proposed modified risk information, participants perceived VLN™ cigarettes as presenting lower risks of tobacco-related diseases compared to other cigarettes, including lung cancer and 17 other tobacco-related health effects. However, in the applicant's research, the survey questions did not specify frequency of use, and the research did not assess the assumptions participants made in answering disease risk questions (e.g., whether they assumed they would use the proposed MRTPs to reduce smoking). Therefore, it is unclear whether these perceptions reflect consumer misperceptions of toxicity or correct consumer understanding of the reasonably likely reduction in disease risks resulting

from using VLN™ cigarettes, which are less addictive, and would lead to smoking fewer CPD with an increased likelihood of smoking cessation over time. TPSAC committee members stated it was unlikely that participants thought through the products' addictiveness (and the corresponding effects on use frequency, duration, and, in turn, disease risks) when rating the risks of smoking VLN™ cigarettes.

These findings and considerations regarding (c) and (d) underscore the need to recommend that the order require VLN™'s modified risk LLA to include an explicit statement about how the product must be used in order to obtain a benefit (i.e., "Helps you smoke less") in a way that will be noticed and read. Including this statement can help consumers understand how the product is used (i.e., to reduce smoking), which ensures their understanding of health risk reduction in line with what is reasonably likely to be demonstrated in subsequent studies. Additionally, by including this statement, the LLA will enable consumers to clearly understand the significance of the reduced nicotine claims, the relevance to their personal health (or the irrelevance, if the person does not wish to smoke less), and the reason why the manufacturer would be providing the information about nicotine to consumers.

Under section 911(g)(2)(B)(iii) of the FD&C Act, to issue an exposure modification order, FDA must find 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 *is or has been demonstrated* to be less harmful or *is or has been demonstrated* to present less of a risk of disease than one or more other commercially marketed tobacco products. FDA interprets this to mean finding that consumers do not hold inaccurate beliefs or are not misled regarding the definitiveness of the evidence regarding the relative risks or harm of the product. The totality of evidence on consumer understanding supports that if the LLA include the statement "helps you smoke less," the LLA enable consumers to understand: (1) the explicit meaning of the proposed modified risk information; (2) the VLN™ cigarettes' conditions of use; (3) the addiction risk; and (4) the health risks aside from addiction. Thus, it is my view that the testing of actual consumer perceptions showed that, overall, consumer understanding is generally in line with the health risks of the product that are reasonably likely and the current state of the evidence.

Also, I recommend that the applicant include the disclaimer "Nicotine is addictive. Less nicotine does NOT mean safer…" on the VLN™ cigarette pack if the LLA include one or more of the authorized exposure claims, given that it was present on all of the labeling that the applicant tested in its quantitative consumer research. However, the social science review notes that several aspects of the disclaimer are inconsistent with expert recommendations for disclaimers, and prior research suggests that poorly designed disclaimers can confuse consumers and change their perceptions, attitudes, or decisions in a manner opposite of that intended (Green & Armstrong, 2012). Since the applicant submitted no evidence about the disclaimer's independent effect on consumer understanding, I also recommend that the order require that the applicant conduct a postmarket study to provide FDA with evidence about the disclaimer. Such a study can provide evidence of whether the disclaimer helps enable consumers to understand that VLN™ cigarettes present the same disease risks as other cigarettes if smoked in the same way, or whether the disclaimer confuses people about the health risks of VLN™ cigarettes.

Population health impact

Regarding population health impact, the available scientific evidence demonstrates that the issuance of an exposure modification order for the proposed MRTPs would be appropriate to promote the public health and 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. The social science review found that after viewing product labels with the exposure reduction claims, many current smokers were interested in VLN™ cigarettes (mean intentions were above the midpoint of the scale), and smokers had significantly higher intentions to purchase the proposed MRTPs compared to Marlboro Gold cigarettes. Current smokers also reported substantially higher intentions to use VLN™ cigarettes on a regular, ongoing basis compared to Marlboro Gold™. Additionally, adult never smokers and former smokers had low intentions to buy and use VLN™ (mean intentions were near the bottom of the scale), and these intentions were similar to or slightly higher than their intentions to buy and use Marlboro Gold.™

Additionally, the epidemiology review evaluated the applicant's population model estimating the public health impacts of the proposed MRTPs. The model assumes that the market share of conventional cigarettes (CC) and VLN™ will be equalized at around 25% by year 2050, meaning that approximately 7.1% of CC smokers will initiate VLN™ smoking per year (i.e., if 7.1% of CC smokers switch to VLN™ cigarettes every year until 2050, then at least 25% of smokers will be using VLN™ cigarettes by 2050). Some model inputs were based on clinical studies; in a real-world setting, the uptake of VLN™ cigarettes among current smokers could be low. Thus, the projected benefits may be overestimated (e.g., high projected market share, dual users of CC and VLN™ cigarettes). Still, overall, epidemiology concluded that there are likely to be some benefits of smokers switching to VLN™ cigarettes and low uptake by nonusers.

These findings are consistent with other reviews' findings supporting a population health benefit:

- The BCP review found that smokers who predominately used the proposed MRTPs significantly reduced their CPD over time, and the CPD of smokers assigned to switch to the proposed MRTPs was half that of smokers assigned to use UB-NNC cigarettes. Reviewers found that using the proposed MRTPs would be reasonably likely to reduce nicotine dependence.

- The BCP review found that the proposed MRTPs have a low abuse liability, similar to NRT, reducing the risk that tobacco nonusers who initiate VLN™ use will have difficulty quitting the product.

- The epidemiology and medical reviews found that a reduction in CPD of at least 50% is associated with a reduction in some tobacco-related diseases (e.g., lung cancer) but not others.

Under section 911(g)(2)(A)(iii) of the FD&C Act, to issue an exposure modification order, FDA must find "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 set forth in [section 911(g)(1)]." The available evidence is not sufficient to conclude that the applicant has demonstrated that the products, as 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." There are no long-term epidemiological studies on cigarette consumption among VLN™ cigarette smokers and the CPD consumption evidence provided by the applicant was based on clinical studies where NNC smokers, with no intention to reduce their nicotine consumption nor quit smoking, were instructed to switch to use VLN™ cigarettes. It is not clear how well CPD findings from clinical

studies will generalize to a real-world setting; they could be overestimates or underestimates. Thus, there are outstanding questions about the manner in which consumers will use VLN, and if individual tobacco users use VLN cigarettes in the same frequency and manner as conventional cigarettes, they will not significantly reduce harm and their risk of tobacco-related disease. In addition, while the applicant-sponsored studies do not address biomarkers of potential harm (BOPH), one published study on the effect on BOPH of switching from conventional cigarettes to VLNC cigarettes was submitted (Hatsukami et al., 2019). This study did not identify robust changes between the study groups; therefore, no conclusions regarding the short- or long-term health risk of VLN™ cigarettes can be made based on the available BOPH data. In totality, conclusive scientific evidence to meet the standards set forth in section 911(g)(1) is not available.

However, it is reasonably likely that cigarette smokers who use VLN cigarettes will experience a reduction in nicotine dependence, which will also reduce tobacco dependence. Reductions in tobacco dependence can lead to increased tobacco cessation and are anticipated to lead to long-term reductions in exposure to the smoking-related toxicants associated with morbidity and mortality. Using the proposed MRTPs would be *reasonably likely* to reduce nicotine dependence and a reduction in CPD of at least 50% is associated with a reduction in *some* tobacco-related diseases (e.g., lung cancer), but not others, supporting a likely overall population health benefit.

Additionally, the social science review describes some information suggesting that, depending on how VLN™ cigarettes are marketed, effects on youth may be limited. For example, youth cigarette smoking rates declined while Quest cigarettes were on the U.S. market and advertised as “low nicotine,” “extra low nicotine,” and “nicotine free.” Furthermore, one study found that after viewing ads for Quest, Marlboro cigarettes, and a heated tobacco product, college students rated Quest cigarettes as lowest on a scale of positive expectancies (e.g., “satisfying,” “fun”) that predicted willingness to try each product (O’Connor et al., 2007). However, given that youth are at increased risk, generally, for initiating tobacco use and the potential effect of modified risk information on youth use, it is critical that any marketing plans be designed to prioritize preventing youth exposure. Studies suggest that perceptions of risk predict tobacco product use among youth (Song et al., 2009) (Strong et al., 2019). FDA’s PMTA marketing authorization order for the products includes postmarket requirements to help ensure that youth exposure to tobacco marketing is being limited. This includes implementing plans to restrict youth access and limit youth exposure to the products’ labeling, advertising, marketing, and/or promotion, and requiring the applicant to track and measure actual delivery of all advertising impressions, including among youth. In addition, as described below, postmarket surveillance and studies should be conducted to monitor youth awareness and use of the proposed MRTPs to ensure that their marketing will not have the unintended consequence of leading to increased use of these products among youth.

I recommend that this exposure modification order include both VLN™ King and VLN™ Menthol King combustible cigarettes. Although FDA announced in May 2021 that it would develop a proposed rule regarding menthol in cigarettes, menthol cigarettes are currently legal tobacco products in the marketplace and Moonlight Menthol cigarettes were previously found to be appropriate for the protection of public health (APPH) in that context. VLN™ Menthol King is identical to Moonlight Menthol, which was authorized under section 910 of the FD&C Act. FDA authorized the marketing of the Moonlight and Moonlight Menthol combustible cigarettes without modified risk claims on December 17, 2019. This review has found that an exposure modification order for both products would be appropriate to promote public health and is expected to benefit the health of the population as a whole, including VLN™ Menthol King cigarettes, which will provide a reduced nicotine option for menthol NNC

cigarette smokers. This recommendation considers the current marketplace without a rule regarding menthol cigarettes in effect; the previous authorization under section 910 of the FD&C Act for Moonlight Menthol cigarettes, which are identical to VLN™ Menthol King cigarettes; and the reduced nicotine option that an exposure modification order would provide for menthol cigarette smokers in the current marketplace.

Section 911(g)(2)(C)(i) of the FD&C Act provides that an MRTP exposure modification order shall be limited for a term of not more than 5 years. I recommend authorization for a period of 5 years, given the low abuse liability of these products. Although this review has found that an exposure modification order for the products would be appropriate to promote the public health and is expected to benefit the health of the population as a whole, that determination may change over time as a function of how the products are actually used by consumers as well as how the marketplace changes. Therefore, monitoring use of the proposed MRTPs in terms of uptake, dual use, and complete switching should be required, including the potential for initiation among youth. As described below, postmarket surveillance and studies should be required in the order to include an assessment of MRTP users' behavior and understanding over time. A 5-year period is a reasonable amount of time to assess whether there is appropriate consumer understanding and to generate preliminary data on behavior in postmarket surveillance and studies to assess whether the standard continues to be met and whether the order should be renewed. In addition, the order should require a study on the independent effects of the disclaimer; it is unclear whether the disclaimer benefits or reduces consumers' ability to understand the risks of using the proposed MRTPs.

II. Regulatory Information

A. 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 25, 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.

- March 2, 2020: an amendment containing a tabular index of citations for the company's MRTPAs.

- March 10, 2020: an amendment submitting the applicant's new tables VI.F-1, VIG-1, and VI.G-2 for the Environmental Assessment for their MRTPAs.

- February 5, 2021: an administrative amendment (b) (4) (b) (4)

Under section 910 of the FD&C Act, the applicant requested authorization to market Moonlight and Moonlight Menthol[1] combustible cigarettes without modified risk claims. FDA authorized the marketing of Moonlight and Moonlight Menthol[1] combustible cigarettes without modified risk claims on December 17, 2019. The TPL review for the accompanying PMTAs provides detail on the engineering, chemistry, stability, and manufacturing of the products, including the results of FDA inspections of manufacturing sites, and is available at: https://www.fda.gov/tobacco-products/premarket-tobacco-product-applications/premarket-tobacco-product-marketing-orders. Where relevant, the present review reflects determinations made in the PMTA TPL review.

The focus of this review of the MRTPAs is on the assessment of (1) the proposed modified risk claims, (2) relative health risks of the products, (3) consumer understanding, and (4) potential impact to the population from marketing the products with the proposed modified risk information.

B. Proposed Modified Risk Tobacco Product

1. Proposed Modified Risk Claims

The applicant requested MRTP orders under section 911(g)(2) of the FD&C Act. The applicant proposed to disseminate the following three reduced exposure claims in the LLA for VLN™ cigarettes (Section V "Labels, Labeling, and Advertising," p. 3):

Exposure Modification Order Request Under 911(g)(2):

- Claim #1: "95% less nicotine"

- Claim #2: "Helps reduce your nicotine consumption"

- Claim #3: "...greatly reduces your nicotine consumption."

In addition to disseminating this modified risk information on VLN™ cigarette packs, cartons, and cases, the applicant also proposed to disseminate this modified risk information in advertisements. The proposed advertising channels include a branded website, print ads, digital ads, direct mail, email, social media, brochures, point-of-sale ads, and earned media (Section V "VLN™ Marketing Outline," p. 1). The applicant submitted screenshots of its draft website and examples of ads for each channel (Section V

"VLN™ Marketing Outline," pp. 3-41). FDA examined the applicant's marketing examples and identified seven additional reduced exposure claims, in addition to Claims #1-3 described above:

- Claim #4: "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 0.27 mg of nicotine."

- Claim #5: "Without exception, VLN™ cigarettes contain at least 95% less nicotine than the top 100 cigarette brands in the United States."

- Claim #6: "22nd Century's VLN™ cigarettes contain an average of 0.27 mg nicotine - -at least 95% less nicotine compared to conventional cigarettes."

- Claim #7: "22nd Century's VLN™ cigarettes feature the same nicotine content as the lowest nicotine style of the Company's SPECTRUM research cigarettes."

- Claim #8: "VLN™ cigarettes contain 0.27 ± 0.1 mg nicotine."

- Claim #9: "As a result of our unique technology and plant breeding expertise, VLN™ tobacco grows with 95% less nicotine than conventional tobacco."

- Claim #10: Several examples utilize a graph depicting nicotine levels of VLN™ cigarettes compared to several other cigarette brands.

These statements appear to convey the same type of information as Claims #1-3. Specifically, the claims are limited to information about VLN™ cigarettes' nicotine content and how it compares with that of other cigarettes, although some of the claims describe the nicotine content in absolute terms (e.g., ".27 mg"), use qualitative comparisons (e.g., "substantially lower"), or include comparators (e.g., "the top 100 cigarette brands").

The labels and most of the advertising also include the following disclaimer: "Nicotine is addictive. Less nicotine does NOT mean safer. All cigarettes can cause disease and death."

2. Description of Product

The decision summary for the PMTA reviews of this product is included the product description below.

The applicant's VLNC tobacco was developed in 1998 and has been used for producing cigarettes under different names, including SPECTRUM and PARE. The SPECTRUM product line consists of a series of cigarette styles that vary in nicotine content, from very low (0.4 mg/g tobacco) to relatively high (15.8 mg/g tobacco) nicotine content. SPECTRUM products are available for research in 24 styles, in both regular and menthol versions, with eight levels of nicotine in their tobacco. SPECTRUM cigarettes are made with NNC tobacco and VLNC tobacco.

PARE cigarettes were developed by 22nd Century for potential marketing in the U.S. pursuant to a premarket authorization in 2015 and were subsequently withdrawn. The applicant states that the PARE products are the same as the VLNC versions of SPECTRUM cigarettes (NRC102 and 103). Most recently, 22nd Century developed the VLN™ cigarettes that are the subjects of these applications. According to the

applicant, VLN™ cigarettes are "exactly the same as the NRC102 and NRC103 SPECTRUM VLNC research cigarettes. They are also the same as the PARE cigarettes that were the subject products of the previous applications. The only difference between each respective regular or menthol VLN™, PARE and SPECTRUM NRC102/NRC103 brand style is the name of the product."

Unlike typical American blended cigarette tobacco, which contains a mixture of Bright, Burley, Oriental, and reconstituted tobaccos, (b) (4) . The two VLN™ cigarette tobacco products contain an (b) (4) tobacco blend that consists of approximately (b) (4) (b) (4) and (b) (4) . The blend also contains (b) (4) (b) (4)

The applicant states that Vector 21-41 tobacco is a unique tobacco variety not present in any commercially-marketed cigarette tobacco. The tobacco has been genetically engineered using the applicant's proprietary technology to block several genes that result in suppression of nicotine biosynthesis. The VLN™ cigarette tobacco products containing Vector 21-41 VLN™ tobacco blend have a target filler nicotine specification of (b) (4) mg/g of tobacco on a DWB, with an upper limit of (b) (4) mg/g and a per-cigarette target of 0.27 mg (± 0.10mg). The applicant reported that the tobacco nicotine content of all 10 batches of the two new VLN™ cigarettes met a maximum nicotine specification o (b) (4) mg/g on a DWB. Furthermore, batch analysis of eight batches of VLN™ cigarettes shows a slightly higher nicotine content than the 0.27 mg/cig reported by the applicant. The measured average VLN™ nicotine content was 0.29 mg/cig. However, this is within the advertised nicotine content lower and upper limit of 0.27 ± 0.10 mg/cig (0.17 and 0.37 mg/cig lower and upper limit).

A more detailed description of the product by FDA, including ingredients, manufacturing process, FDA sample testing, and product stability information, can be found in the PMTA TPL review for the same products.[6]

C. Tobacco Products Scientific Advisory Committee (TPSAC)

Pursuant to section 911(f) of the FD&C Act, FDA referred the MRTPAs to TPSAC, and TPSAC reported its findings on the applications during an open public committee meeting held on February 14, 2020. At the meeting, the committee discussed the MRTPAs, including: consumer understanding of the labeling; the likelihood that reductions in dependence translate into reductions in morbidity and mortality; and likelihood of use among current, former, and never cigarette smokers. Information about the meeting, including the complete transcript, is available at: https://www.fda.gov/advisory-committees/tobacco-products-scientific-advisory-committee/2020-tpsac-meeting-materials-and-information

FDA shared its preliminary assessment of the applications with the committee, focusing on: the scientific substantiation of the proposed modified risk claims; consumer understanding and perceptions of the proposed modified risk information; impact on morbidity and mortality; and impact on current cigarette smokers and nonsmokers. TPSAC was asked to discuss FDA's preliminary assessment, including (1) the likelihood that reductions in dependence translate into substantial reductions in morbidities and

[6] https://www.fda.gov/tobacco-products/premarket-tobacco-product-applications/premarket-tobacco-product-marketing-orders

mortality among individual tobacco users; (2) the extent to which never and former cigarette smokers are likely to try and progress to regularly using the proposed MRTPs; (3) the extent to which the cigarette smokers who do and do not want to quit will dual use the proposed MRTPs with their usual brand of cigarettes or exclusively use the proposed MRTPs; and (4) whether the labeling enables consumers to accurately understand the disease and addiction risks of using the products. A summary of TPSAC's discussions, organized by these four topic areas, is presented below. FDA's assessment of these discussions is included in Section III of this review, as well as in individual discipline reviews.

1. The likelihood that reductions in dependence translate into substantial reductions in morbidities and mortality among individual tobacco users.

TPSAC discussed questions about biomarkers and topographical data and whether enough data were available to substantially conclude that a reduction in dependence would then translate into a reduction in morbidity and mortality.

One member said they thought that a reduction in smoking was likely to translate to a reduction in morbidity and mortality. Another member stated that there are actually two pathways to reduced morbidity and mortality: one is the reduction in cigarettes per day, and the other pathway is the reduction in dependence, which can lead to an increase in cessation. Another member noted that while there was a dose-response relationship for cancer, there was no such relationship for cardiovascular disease (CVD). Another agreed that not all morbidities would be reduced. I agree with their assessment; my assessment of the effects of using the product on morbidity and mortality can be found in Section (III)(B) of this review.

The committee noted that the clinical studies on VLNC instructed participants to switch completely to VLNC cigarettes. Without instructions for VLN™ cigarette use, results obtained in these clinical studies are likely not representative of a situation in which individuals do not receive instructions for use. The committee recommended that information be added to VLN™ cigarettes to clarify that smokers should switch completely to the products in order to achieve results similar to those obtained in the clinical literature. The committee also discussed the dual use issue. While I agree there is some uncertainty in how clinical study findings will generalize to the real-world setting, I also note that dual use of VLNCs with UB-NNC was very common in clinical settings; smokers who did this, but predominately used VLNCs, were still able to benefit from using VLNCs. My discussion of this can be found in Section (III)(B) of this review.

In summary, TPSAC discussed that there seemed to be some compelling information to make the inference that as dependence declines due to VLNC use, other things such as behavioral and physiological changes can follow, which may lead to some reductions in morbidities and likely lead to a reduction in mortality at the individual level.

2. The extent to which never and former smokers are likely to try and progress to regularly using the proposed MRTPs.

The committee expressed concerns about there being no evidence with testing or clinical data about use among young people. TPSAC members stated that they would like some kind of strategy developed to collect data from youth regarding these kinds of MRTPs, noting that there is a need for adolescent data, but that there are ethical issues with conducting this research.

The committee discussed the difference between trial and experimentation and progression to use. Although there are no direct data about product use among adolescents, there are data from adolescent models and other adult users to suggest that the lower nicotine products would not result in higher abuse liability among youth or adults, compared to normal nicotine level products. The committee felt that progression beyond initial trial to regular use of this product would be unlikely among never smokers, including youth. One committee member also stated that they thought former smokers would not be interested in the product and did not have concerns about relapse among them. Some TPSAC members noted that there is a lack of data and that more data are needed to draw conclusions on the likelihood of progression to either continued VLN™ or conventional cigarette use after experimentation with VLN™ cigarettes. I agree with the overall assessment that the likelihood of nonuser initiation is low and discuss this in Section (III)(D)(3).

TPSAC expressed concerns regarding the advertising and imagery being appealing to youth. (b) (4) [redacted]. There was discussion regarding the brand name of Moonlight and the committee mentioned that the word "light" has come up before in previous meetings. FDA staff clarified that the application review is for products names VLN™ cigarettes, not Moonlight.

3. The extent to which cigarette smokers (who do and do not want to quit) will dual use the proposed MRTPs with their usual brand of cigarettes or exclusively use the proposed MRTPs.

TPSAC discussed how compliance might differ among smokers who do want to quit, noting that the committee members' clinical studies on the topic did not look at this. TPSAC discussed that the probability of dual use is likely high in scenarios where both usual brand cigarettes and low nicotine content cigarettes are available. Dual use may occur for both smokers who want to quit and smokers who do not want to quit, and the extent of dual use may vary. TPSAC discussed that cigarette smokers who do not want to quit smoking may dual use VLN™ and usual brand cigarettes, believing that dual use may reduce their nicotine exposure and lower their health risks. They discussed that smokers who do want to quit may use the product on the road to quitting.

TPSAC discussed that instruction of completely switching is missing, and if this information/instruction was provided, or clearer, it could potentially decrease dual use and cigarette-related diseases.

While I agree that there is some uncertainty in how clinical study findings will generalize to the real-world setting, I also note that dual use of VLNCs with UB-NNC was very common in clinical settings. Smokers who did dual use, but predominately used VLNCs, were still able to benefit from using VLNCs. My discussion of this can be found in Section (III)(B) of this review.

4. Whether the labeling enables consumers to accurately understand addiction and disease risks of using the products.

Regarding addiction risk, TPSAC generally agreed that the labeling would enable consumers to understand the addiction risk from smoking VLN™ cigarettes. However, one member pointed out that addiction risk is different for everyone; that is, it's not all equal. There are data to support this in genetic

studies. Therefore, the response to nicotine and perceptions of risk will differ from individual to individual.

Regarding disease risks, TPSAC discussed the applicant's study results showing that U.S. adults rated VLN™ cigarettes as lower in disease risks compared to other cigarettes. FDA presented two alternative interpretations of these findings to TPSAC and asked for committee members' perspectives on whether one of these interpretations was more likely to be correct than the other: (1) participants *incorrectly* rated VLN™ cigarettes as lower in disease risks than other cigarettes because participants believed the lower nicotine content would allow people to smoke VLN™ cigarettes in the same way as other cigarettes without incurring the same disease risks, or (2) participants *correctly* rated VLN™ cigarettes as lower in disease risks than other cigarettes because participants understood that, because of VLN's lower addiction risk, people would smoke fewer VLN™ cigarettes or would smoke VLN™ for a shorter duration than other cigarettes, causing fewer diseases. TPSAC members stated that the first interpretation is more likely to be correct, because it is unlikely that participants thought through the products' addictiveness (and the corresponding effects on use frequency and duration) when rating the disease risks of smoking VLN™ cigarettes. TPSAC members suggested that participants' lower ratings of disease risk from VLN™ cigarettes could be attributed to widespread misperceptions of nicotine, and that the proposed VLN™ labeling would not enable consumers to understand the products' disease risks.

Three members noted issues with the disclaimer/ "voluntary warning" and the need for more research on this warning. One member said more research is needed on what might reduce misperception of disease risk, because the "voluntary warning" is not sufficient. Another said that the "voluntary warning" was problematic because it looks like a legal disclaimer and there was no evidence of its impact. Another said there was a need to test ways to communicate that the product is equally risky, such as several reasonable strategies tested with the most promising one selected.

There was consensus on the importance of providing accurate, specific information to the public about nicotine content, and that there are important benefits to educating the public about nicotine. The committee also noted, though, that nicotine misperceptions are common and that no one product is likely to overcome all the existing misperceptions about risk. Most members agreed that information about the product being low nicotine should not be withheld. Generally, I agree with this assessment, and my evaluation of consumer understanding is presented and discussed in Section (III)(C) of this review.

D. Public Availability of MRTPAs

Pursuant to section 911(e) of the FD&C Act, FDA made the applicant's MRTPAs available to the public (except matters in the applications that are trade secrets or are otherwise confidential, commercial information). The docket for public comment on the MRTPAs for 22nd Century's VLN™ King, VLN™ Menthol King, Combusted, Filtered Cigarettes was open from July 25, 2019, to May 18, 2020. FDA received 226 unique public comments from individuals, academia, health professionals, state and local governments, and other organizations. In addition to legal and advocacy issues, the comments included perspectives on consumer understanding, concerns about a lack of youth data, critiques of the applicant's studies and interpretation of findings, concerns about potential appeal to youth, and concerns about marketing and advertising strategies. Many of the issues and concerns raised in the

public comments were also identified during FDA's scientific review of the applications; these issues are presented and discussed in discipline reviews. FDA considered all significant comments when making the final determination.

We note that some comments pertained to the brand name "Moonlight" for the product, which is the subject of the PMTAs authorized in December 2019. Because the proposed brand name for these applications is VLN™, we do not discuss or address these comments here or in discipline reviews.

III. Summary of Scientific Evidence

The applicant argues that the proposed MRTPs represent a less harmful alternative for current cigarette smokers by providing evidence that the product contains about 95% less nicotine compared to conventional cigarettes on the market. They also provide evidence from: analyses of mainstream smoke HPHCs; nonclinical studies from the literature; and applicant and peer-reviewed clinical studies assessing CPD and BOE over 6 to 20 weeks. This section assesses the evidence on the relative health risks to individual users, including assessment of the scientific accuracy of the modified risk information proposed to be communicated by the applicant to consumers. Subsequent sections of the review address consumer understanding and perceptions of the proposed modified risk information and the potential impact of the products on the population as a whole, including both current users and non-users of tobacco. In our evaluation, we bridge evidence from SPECTRUM NRC 102/103 to the proposed MRTPs.

Throughout this section, I note when evidence provides support for specific proposed modified risk claims. Below is a table summarizing where supporting evidence can be found for each of the applicant-requested Claims (#1-3) and additional FDA identified Claims (#4-10).

Claim	Section of this review with substantiation information
Claim #1: "95% less nicotine"	-Section (III)(B)(1) Nicotine content on a dry weight basis -Section (III)(B)(2)(B) ISO and CI HPHC data -Section (III)(B)(3)(a) Nicotine BOE
Claim #2: "Helps reduce your nicotine consumption"	-Section (III)(B)(2)(B) ISO and CI HPHC data -Section (III)(B)(3)(a) Nicotine BOE
Claim #3: "...greatly reduces your nicotine consumption."	-Section (III)(B)(2)(B) ISO and CI HPHC data -Section (III)(B)(3)(a) Nicotine BOE
Claim #4: "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 0.27 mg of nicotine."	-Section (III)(B)(1) Nicotine content on a dry weight basis
Claim #5: "Without exception, VLN™ cigarettes contain at least 95% less nicotine than the top 100 cigarette brands in the United States."	-Section (III)(B)(1) Nicotine content on a dry weight basis

Claim #6: “22nd Century’s VLN™ cigarettes contain an average of 0.27 mg nicotine - -at least 95% less nicotine compared to conventional cigarettes.”	-Section (III)(B)(1) Nicotine content on a dry weight basis
Claim #7: “22nd Century’s VLN™ cigarettes feature the same nicotine content as the lowest nicotine style of the Company’s SPECTRUM research cigarettes.”	-Section (III)(A) Bridging from SPECTRUM NRC102/103 research cigarettes to VLN™ Cigarettes
Claim #8: “VLN™ cigarettes contain 0.27 ± 0.1 mg nicotine.”	-Section (III)(B)(1) Nicotine content on a dry weight basis
Claim #9: “As a result of our unique technology and plant breeding expertise, VLN™ tobacco grows with 95% less nicotine than conventional tobacco.”	-Section (III)(B)(1) Nicotine content on a dry weight basis
Claim #10: Graphs depicting nicotine levels of VLN™ cigarettes compared to several other cigarette brands.	-Section (III)(B)(1) Nicotine content on a dry weight basis

A. Bridging from SPECTRUM NRC102/103 research cigarettes to VLN™ Cigarettes

Numerous clinical and nonclinical studies have been conducted using VLNC cigarettes. SPECTRUM research cigarettes NRC102 and its mentholated version NRC103 are among the VLNC products often studied in clinical research. Like the two new VLN™ cigarettes, Spectrum NRC102 and NRC103 also contain a tobacco filler with reported nicotine content of 0.5 mg/g on a DWB. The applicant states that SPECTRUM NRC102 is the same as VLN™ King cigarette, and SPECTRUM NRC103 is the same as VLN™ Menthol King cigarette. To bridge clinical data of Spectrum NRC102 and NRC103 to VLN™ King and VLN™ Menthol King cigarettes, respectively, their characteristics are compared and evaluated. Note that the main product performance attributes of VLNCs such as SPECTRUM cigarettes are nicotine and HPHC smoke yields.

The chemistry review compared reported design features and product materials between SPECTRUM and VLN™ cigarettes. The cigarette weight, cigarette length, cigarette diameter, and tipping paper permeability are the same between SPECTRUM and VLN™ cigarettes. The two products also share many of the same components and materials including tobacco type, tobacco blend, cigarette paper, filter, seam adhesive, and tipping adhesive. The only material difference is that the SPECTRUM tipping paper has a silver line and the name SPECTRUM printed on it, whereas the VLN™ tipping paper does not have any markings. The base tipping paper for both tobacco products has the same porosity (b) (4) CU) and is produced by the same manufacturer, (b) (4) . The slight difference in tobacco weight (<2%) is not expected to significantly affect smoke deliveries. Ventilation levels appeared different in testing: 30% for SPECTRUM and 12.5% (target level) for VLN™ cigarettes. BCP evaluated the ventilation levels and determined that from the BCP perspective this difference in ventilation does not raise a concern. While the majority of information on BOE came from the SPECTRUM cigarette literature, the applicant-provided clinical studies show evidence of similar nicotine exposure, non-nicotine HPHC exposure, use behaviors, and subjective effects between VLN™ and SPECTRUM VLNC cigarette smokers. As nicotine is the driver of addiction, there is significantly lower nicotine delivery from VLN™ products and reduced abuse liability (e.g., satisfaction, liking) compared to UB-NNC cigarettes, similar to what is observed with SPECTRUM cigarettes. Although some HPHC yields are different, the reduction in non-nicotine BOE is based on the reduced content of some HPHCs in VLN™ products compared to conventional cigarettes, and on how people use the product (i.e., dependent upon smokers reducing their CPD). There is no evidence to suggest that individuals would use VLN™ products differently than SPECTRUM cigarettes. Therefore, the non-nicotine BOE reported in the SPECTRUM cigarette literature may be extrapolated to the VLN™ products. Although machine measured HPHC yields are slightly higher in VLN™ products compared to SPECTRUM, we expect people who switch to VLN™ products to smoke fewer cigarettes than their UB-NNC cigarettes. This would lead to reductions in BOE compared to UB-NNC cigarettes, and likely be comparable to the levels of BOE reported in SPECTRUM studies.

The reported nicotine smoke yields of SPECTRUM NRC102 and NRC103 are slightly lower than those of VLN™ King and VLN™ Menthol King under both the ISO and CI smoking regimens (0.02 mg/cig and 0.04 mg/cig vs. approximately 0.025 mg/cig and 0.056 mg/cig, respectively). The nicotine deliveries of SPECTRUM NRC102 and NRC103 cigarettes are overall similar to those of VLN™ King and VLN™ Menthol King, respectively, relative to NNC cigarettes. Reported carbon monoxide (CO) yields are equivalent between SPECTRUM NRC102 and NRC103 cigarettes and VLN™ cigarettes. Thus, SPECTRUM NRC102 and NRC103 are considered similar to VLN™ King and VLN™ Menthol King, respectively, based on tar, nicotine, and carbon monoxide (TNCO) deliveries, which are the main product performance attributes.

Therefore, clinical and nonclinical data of SPECTRUM NRC102 and NRC103 cigarettes, which are based mainly on TNCO smoke yields and tobacco nicotine content, may be bridged to VLN™ King and VLN™ Menthol King cigarettes respectively.

For other HPHCs, SPECTRUM NRC102 and NRC103 and VLN™ cigarettes generated similar smoke yields of crotonaldehyde under the ISO smoking regimen and acetaldehyde under the CI smoking regimen. Additionally, SPECTRUM NRC102 and VLN™ King generated similar smoke yields of acrolein and benzo[a]pyrene under the ISO smoking regimen, as well as acrolein, 1-aminonaphthalene, and NNK under the CI smoking regimen. SPECTRUM NRC102 and NRC103 cigarettes generated considerably higher smoke yields of most other HPHCs including benzo[a]pyrene compared to VLN™ King and VLN™ Menthol King respectively, which do not raise concerns for the VLN™ cigarettes. In contrast, SPECTRUM NRC102 and NRC103 cigarettes generated lower smoke yields of 4-aminobiphenyl and NNN under the ISO smoking regimen, and crotonaldehyde, formaldehyde, and NNN under the CI smoking regimen. Although the noted HPHC differences should be considered when bridging clinical and nonclinical data, the differences in these other HPHC yields do not raise concerns. Moreover, the chemistry review notes that the differences in the HPHC data between VLN™ and SPECTRUM cigarettes may be attributable to samples manufactured and tested four years apart using two different laboratories. If the applicant wishes to retest mainstream smoke HPHCs of VLN™ and SPECTRUM cigarettes for HPHC data comparison, FDA suggests that appropriate testing measures be taken including, but not limited to, using the same laboratory, the same methods, similar sample storage conditions and duration, and testing within a similar timeframe to minimize HPHC data variability.

Based on the overall product design features, components, materials, tobacco type, tobacco blend, tobacco filler nicotine, nicotine and tar deliveries, and many equivalent mainstream smoke HPHCs, SPECTRUM NRC102 and NRC103 research cigarettes are considered similar to VLN™ King and VLN™ Menthol King cigarettes. In this review, the terms SPECTRUM NRC102/103 cigarettes and VLNC cigarettes are used interchangeably.

This evidence supports Claim #7, "22nd Century's VLN™ cigarettes feature the same nicotine content as the lowest nicotine style of the Company's SPECTRUM research cigarettes."

B. Relative Health Risks of the Proposed MRTPs to Individual Tobacco Users

In my evaluation of health risks to individual tobacco users, I also evaluated several lines of evidence for whether they supported the applicants' statements in the applications related to: (1) nicotine content; (2) HPHCs; (3) BOE and the toxicology assessment; and (4) clinical studies examining dependence, abuse liability, CPD, and adverse health effects.

1. Nicotine content on a dry weight basis (DWB)

The applicant states that Vector 21-41 tobacco is a unique tobacco variety not present in any commercially-marketed cigarette tobacco. The tobacco has been genetically engineered using the applicant's proprietary technology to block several genes that result in suppression of nicotine biosynthesis. The VLN™ cigarette tobacco products containing Vector 21-41 VLN™ tobacco blend have a

target filler nicotine specification of (b) (4) mg/g of tobacco on a DWB, with an upper limit of (b) (4) mg/g and a per-cigarette target of 0.27 mg (± 0.10mg).

The applicant provided a survey of 100 top-selling cigarette brands that represent 87% of all cigarettes sold in the U.S. through convenience stores in 2017. See Section VIIIB-1ii of the MRTPAs for a description of these 100 cigarette brands. These 100 cigarettes contain a reported average of 19.4 mg nicotine per gram of tobacco on a DWB, and a reported average of 12.0 mg nicotine per cigarette. The applicant reported that tobacco nicotine content of all 10 batches of the two new VLN™ cigarettes met their maximum nicotine specification of (b) (4) mg/g on a DWB, and 0.27mg ± 0.10 nicotine per cigarette. Accordingly, the reported nicotine contents of the VLN™ cigarettes are 98% lower than the average reported nicotine contents of the top 100 cigarette brands determined both per gram of tobacco and per cigarette.

The applicant also compared the two new VLN™ cigarettes to the four top-selling king-sized regular cigarette brands and two top-selling king-sized mentholated cigarette brands. These cigarette brands, whose unit sales rank is shown in parentheses, are Marlboro Gold King (1), Marlboro Red King (2), Newport Menthol Green King (4), Marlboro Special Blend Gold King (5), Camel Blue King (8), and Marlboro Menthol Gold King (17). The six top-selling king-sized cigarette brands contain a reported average tobacco filler nicotine content of 18.8 mg/g on a DWB and a reported average of 11.0 mg nicotine per cigarette. The applicant reported tobacco nicotine content of all 10 batches of the two new VLN™ cigarettes met their maximum nicotine specification of (b) (4) mg/g on a DWB and 0.27 mg nicotine per cigarette. Thus, the reported nicotine contents of the VLN™ cigarettes are at least 97% lower than the average nicotine contents of the top six king-sized cigarette brands determined both per gram of tobacco and per cigarette.

Overall, this information provides support for the required finding in 911(g)(2)(B)(i) that "the magnitude of the overall reductions in exposure to the substance or substances 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 or substances"; and also provides support for Claim #1 and Claims #4-10 regarding the nicotine content of the proposed MRTPs.

2. Harmful and Potentially Harmful Constituents (HPHCs) and Toxicology Evaluation

a. General Overview

The applicant tested and reported HPHC data including all abbreviated HPHCs recommended for cigarette mainstream smoke under both International Organization for Standardization (ISO) and Canadian Intense (CI) machine smoking regimens (Chen et al., 2014). The applicant also reported mainstream smoke HPHCs for the six market-leading king-sized cigarette brands measured under the ISO smoking regimen. The applicant obtained CI HPHC data for the six comparator cigarette brands from the HPHC reports submitted by tobacco manufacturers pursuant to section 904(a)(3) of the FD&C Act.

The HPHCs in the two VLN™ cigarettes and six comparator cigarette brands measured under the ISO and CI smoking regimens were analyzed using the "two one-sided tests" (TOST) methodology to determine

analytical equivalence. For the TOST equivalence test, the recommended important analytical differences are 10% for tar and CO, 15% for nicotine and 20% for other HPHCs.[7]

The VLN™ cigarettes have lower reported yields of many HPHCs including nicotine, acrolein, formaldehyde, benzo[a]pyrene, and TSNAs than the six comparator cigarette brands under the ISO smoking regimen. Reported yields of other HPHCs including menthol are comparable. However, reported ISO regimen smoke yields of acrylonitrile, 4-aminobiphenyl and ammonia are higher for VLN™ King cigarettes, whereas acrylonitrile, 4-aminobiphenyl, ammonia, and benzene yield are higher for VLN™ Menthol King cigarettes. In addition, available CI regimen smoke yields of acrylonitrile, acetaldehyde, and ammonia are higher for both VLN™ cigarettes. As discussed below, toxicology evaluated all provided HPHCs relative to the six conventional cigarette comparison products, and concluded that, "net HPHC exposure from VLN™ cigarettes is similar or lower relative to the comparison products". While some individual HPHC yields from VLN™ cigarettes are higher relative to the comparison products, the net effect of HPHC changes, specifically the net impact of the lower HPHC yields, translates to similar or lower risks in using VLN™ cigarettes relative to the comparison products and therefore conventional cigarettes more broadly. This evaluation provides information about the individual health effects of using the proposed MRTPs, as well as substantiation of claims related to nicotine content.

b. ISO and CI Regimen HPHC Data and Toxicology's Qualitative Assessment

ISO regimen data and qualitative assessment

Per the applicant's submitted ISO regimen HPHC data and Chemistry's TOST analysis, in comparison to the average of the six commercially marketed NNC cigarette comparators, the two VLN™ cigarettes have nonequivalent lower reported yields of many HPHCs including nicotine, acrolein, formaldehyde, benzo[a]pyrene, and TSNAs than the six comparator cigarette brands under the ISO smoking regimen. Specifically, nicotine content is 97% lower in the proposed MRTPs compared to the six comparator products. **This information provides support for Claim #1, "95% less nicotine."** Reported yields of other HPHCs including menthol are equivalent. However, reported smoke yields of acrylonitrile, 4-aminobiphenyl and ammonia are higher and not equivalent for both VLN™ cigarettes, whereas benzene yield is higher and not equivalent only for VLN™ Menthol King.

In both ISO comparisons, acrylonitrile is higher (49% and 55% respectively), 4-aminobiphenyl is higher (21% and 19% respectively) and ammonia is higher (120% and 150% respectively). The applicant states that the significantly higher levels of 4-aminobiphenyl and ammonia are expected side effects of the genetic engineering of the VLN™ burley tobacco. Specifically, the applicant states, "The nicotine and TSNA production pathways in VLN™ tobacco plants are intentionally inhibited. This results in a slight accumulation of ammonia in the plant. It is hypothesized that the plant continues to assimilate nitrogen resulting in an increase in smoke ammonia as well as other nitrogen containing constituents, including 4-aminobiphenyl…." The HPHC data appear to reflect the applicant's statement, as both nicotine and TSNAs are lower, while 4-aminobiphenyl and ammonia are higher.

Regarding the appropriateness of the commercially marketed NNC cigarette comparators, there are differences in design features that may impact mainstream smoke HPHC levels and comparisons.

[7] Division of Product Science Memorandum "Equivalence Testing for SE Evaluations"

However, the applicant appears to employ sufficient selection criteria for marketed comparators, mainly based on market share analysis but also based on some design features. Per the applicant, the combined users of the commercially marketed NNC cigarette comparators represent around 25% of all smokers. In addition, all the products are king size, with similar yet small nuanced differences in lengths and weights that may or may not impact HPHC production. Conversely, filter ventilation, or pores in the filter, which allow for the dilution of mainstream smoke during ISO regimen machine smoking, can tend to lower the expected absolute yields of HPHCs (along with a decrease in puffing volume and increased interpuff interval) (Counts, Morton, Laffoon, Cox, & Lipowicz, 2005; Kozlowski & O'Connor, 2002). Aside from Newport Menthol Green cigarettes (2%) and Marlboro Red cigarettes (10.8%), commercially marketed NNC cigarette comparators have ventilation levels greater than 28%, while the VLN™ cigarettes appear to be ventilated at a level of 12.5%. Thus, in this specific case, increased HPHCs in the VLN™ cigarettes may potentially be overestimated by direct comparison to the averaged HPHC values in the commercially marketed NNC cigarette comparators. Specifically, in describing exposure variables and assumptions in the whole product risk assessment, the applicant included behavioral components such as CPD and puff volume. Nonetheless, based on the individual product comparisons provided in the application, the HPHC differences between VLN™ King cigarettes and Marlboro Red cigarettes, and VLN™ Menthol King cigarettes and Newport cigarettes appear within range of the average values.

Qualitatively, the ISO HPHC mean changes (i.e., relatively higher and lower HPHC yields) can be assessed, in part, based on the carcinogenic and noncarcinogenic effects of each HPHC, the number of lower HPHCs that occur concurrently with higher HPHCs, and the magnitude and potency or effect level of the HPHCs. Qualitative evaluation of relative HPHC changes can indicate whether there may be an increase in potential toxicity between the products, prior to considering a quantitative risk assessment (QRA), which is also discussed below. In both cases—using a qualitative or quantitative approach—the product use behavior is assumed to be the same between the VLN™ cigarettes and the commercially marketed NNC cigarette comparators. This is a conservative approach, given the applicant's submission of two key studies demonstrating a decrease in CPD in users that acutely and completely switch to SPECTRUM NRC102/103 cigarettes, which are nearly identical to the VLN™ cigarettes. Regarding cancer outcomes, the toxicology review noted that higher levels of 4-aminobiphenyl, acrylonitrile, and benzene via the ISO regimen likely do not raise cancer-risk-related concerns for the VLN™ cigarettes. Overall, based on these ISO regimen HPHC data, cancer risks are likely similar with use of VLN™ cigarettes and use of the commercially marketed NNC cigarette comparators. Regarding noncancer outcomes, the higher levels of 4-aminobiphenyl, acrylonitrile, ammonia, and benzene via the ISO regimen likely do not raise noncancer-hazard-related concerns for the VLN™ cigarettes. For example, any increase in respiratory effects due to ammonia and acrylonitrile or increases in cardiovascular effects or reproductive/developmental effects due to benzene, are offset by other HPHCs that are relatively lower and broadly target the respiratory tract, cardiovascular system, and reproductive/ developmental processes. Specifically, these relatively higher level HPHCs occur concurrently with relatively lower levels of the respiratory irritants: formaldehyde, 1,3-butadiene, and acrolein, that offset the increased respiratory hazards due to the higher levels of ammonia and acrylonitrile. Similarly, the increase in cardiovascular and reproductive/developmental effects due to higher levels of benzene tends to be offset by lower levels of nicotine and 1,3 butadiene respectively, although there is some uncertainty given available data used to develop the associated reference values. Overall, based on the ISO regimen HPHC data, noncancer hazards due to use of the VLN™ cigarettes are likely similar to those with use of the commercially marketed NNC cigarette comparators.

The toxicology review determined that overall, based on ISO regimen HPHC data, the noncancer hazards due to use of the VLN™ cigarettes are likely similar to those with use of the commercially marketed NNC cigarette comparators. In addition, based on the ISO regimen HPHC data, cancer risks due to use of the VLN™ cigarettes are likely similar and may be less than those associated with use of the commercially marketed NNC cigarette comparators.

CI regimen data and qualitative assessment

The applicant did not test the mainstream smoke HPHCs of the six comparator cigarette brands under CI conditions. Under a Freedom of Information Act (FOIA) request, the applicant obtained the CI HPHC data of the six comparator cigarette brands from the HPHC reports submitted by tobacco manufacturers pursuant to section 904(a)(3) of the FD&C Act. The VLN™ cigarettes generated lower or comparable reported smoke yields of most HPHCs compared to the six comparator cigarette brands. With respect to nicotine, the reported nicotine smoke yields for the VLN™ cigarettes are 97% lower than the average reported nicotine smoke yield of the six market-leading king size comparator NNC cigarettes. **This information provides support for Claim #1, "95% less nicotine," and Claims #2 and 3 regarding reduced nicotine consumption.** In addition, there are substantially higher amounts of ammonia in both VLN™ cigarettes; there are also moderately higher amounts of acetaldehyde and acrylonitrile smoke yields for both VLN™ cigarettes. These additional reported HPHC increases observed under the CI smoking regimen were evaluated by toxicology for evaluation of health risks.

Per the applicant's submitted CI regimen data and chemistry's TOST analysis, there are three HPHC increases for VLN™ King cigarettes and three increases for VLN™ Menthol King cigarettes in comparison to the average of the six commercially marketed NNC cigarette comparators. In both cases, there are higher levels of ammonia (420% and 490% respectively) as well as acrylonitrile (43% and 44% respectively) and acetaldehyde (33% and 33% respectively). The higher level of ammonia is consistent with the ISO results and likely expected, as stated by the applicant, given its hypothesis around the anticipated increases in nitrogen assimilation that still occur despite genetic modification of the nicotine biosynthesis pathway.

The higher levels of both acrylonitrile and acetaldehyde are consistent with previous reports demonstrating that these HPHCs mainly occur in the gas phase of mainstream smoke, which, on average, tends to be increased relatively more than particulate-phase constituent yields, when comparing CI regimen data to ISO regimen data (Counts et al., 2005). Higher levels of acetaldehyde may be expected given that increases in certain aldehydes are associated with larger puff volumes as well as the lack of ventilation during the CI regimen, which may intensify the combustion of added or natural sugars (Cheah et al., 2018; Pauwels et al., 2018). Lastly, the reductions in TSNAs, nicotine, formaldehyde, acrolein, and benzo[a]pyrene are consistent with the ISO-related results.

While the applicant reported 33% more acetaldehyde in its product compared with the average of the six comparators in the CI measured yields, the values provided for the VLN™ cigarettes and the comparators are all within average values reported in literature for cigarettes in general (Talhout, Opperhuizen, & van Amsterdam, 2007). It is also possible that the 33% higher level of acetaldehyde in the VLN™ products compared to the six commercially marketed cigarettes may be an artifact of the number of comparator products tested. When compared with the acetaldehyde values found in the FDA50, an analysis of 50 popular cigarettes in 2011, conducted by CTP and CDC, there is 6% less acetaldehyde in the VLN™ cigarettes measured under the CI regimen. This is in line with the

comparisons of the ISO regimen values comparing the VLN™ cigarettes with both the six comparator products provided by the company and with the FDA50. Therefore, the 33% higher levels of acetaldehyde found by the applicant in its comparison is not a concern, specifically because of the net HPHC changes indicated for these products that are lower than the comparison products.

Any assumptions pertaining to the discussion of the qualitative ISO evaluations above also apply to the evaluation of CI data here, specifically regarding the potential for carcinogenic and noncarcinogenic HPHCs to offset each other, as well as any available data pertaining to product usage. Conservatively, the VLN™ cigarettes and commercially marketed NNC cigarette comparators are assumed to be used the same by potential users. Specifically, the toxicology review defines VLN™ cigarettes users as completely switching, in acute fashion, from a commercially marketed cigarette. However, as the applicant did not provide evaluation regarding the potential risks based on CI data, discussion pertaining to the potency or degree to which toxic effects may be observed for a given HPHC is based on the magnitude of HPHC changes, and the reference toxicity values as detailed in the toxicology review.

Regarding cancer outcomes, the toxicology review noted that higher levels of acetaldehyde and acrylonitrile via the CI regimen likely do not raise cancer-risk-related concerns for the VLN™ cigarettes. Overall, based on these CI regimen HPHC data, cancer risks are likely similar with use of VLN™ cigarettes and use of the commercially marketed NNC cigarette comparators. Regarding noncancer outcomes, higher levels of acetaldehyde, acrylonitrile, and ammonia via the CI regimen likely does not raise noncancer-hazard-related concerns for the VLN™ cigarettes. For example, any increase in respiratory effects due to ammonia, acetaldehyde, and acrylonitrile are offset by other HPHCs that are relatively lower and broadly target the respiratory tract. Specifically, these relatively higher level HPHCs occur concurrently with relatively lower levels of the respiratory irritants: formaldehyde, 1,3-butadiene, and acrolein that offset the increased respiratory hazards due to higher levels of ammonia, acetaldehyde, and acrylonitrile. Overall, based on the CI regimen HPHC data, noncancer hazards due to use of the VLN™ cigarettes are likely similar to those with use of the commercially marketed NNC cigarette comparators.

This information provides support for the required finding under 911(g)(2)(B)(ii) that “the product as actually used by consumers will not expose them to higher levels of other harmful substances compared to the similar types of tobacco products then on the market unless such increases are minimal and the reasonably likely overall impact of use of the product remains a substantial and measurable reduction in overall morbidity and mortality among individual tobacco users”. In summary, toxicology’s qualitative HPHC evaluation indicates that although there are likely higher exposures to some specific constituents, these higher levels do not appear to impact the overall relative product risks and hazards, given that other constituents associated with similar adverse health outcomes are lower in the VLN™ products compared to conventional cigarettes. The overall health risks and hazards are likely similar or lower in the VLN™ cigarettes versus the comparison products selected by the applicant.

c. Toxicology assessment of applicant-submitted Quantitative Risk Assessment (QRA)

This section summarizes the toxicological studies provided by the applicant to compare the relative toxicity between VLN™ cigarettes and combusted cigarettes. This assessment focuses on non-nicotine mainstream smoke substances (e.g., added ingredients, HPHCs) and whether they raise toxicological

concerns related to Section 911(g)(2)(B)(ii).[8] A summary of these studies and conclusions is presented below. More detailed description and analysis can be found in the toxicology review.

For the applicant-submitted quantitative risk assessment, the VLN™ cigarettes are assumed to be used in the same manner as the comparison products. As such, any differences identified by the applicant in the submitted QRA simply reflect the differences in HPHC yields (i.e., not impacts due to differences in CPD or puffing behavior). The toxicology analysis focused on the HPHC yields, potencies, and magnitudes, concluding that the impact of the higher level HPHC yields for certain constituents were likely not a concern, given the lower level HPHC yields for other constituents with similar associated adverse health effects.

The ISO regimen HPHC data and associated HPHC evaluation discussed in this review tend to support the applicant's QRA conclusions, which are that noncancer hazards and cancer risks are likely similar or lower for users of VLN™ cigarettes compared to those for users of the comparison products. The CI regimen HPHC data and the associated HPHC evaluation likely demonstrate that the noncancer hazards and cancer risks are similar, but the applicant did not submit a separate QRA to support any health risk-related conclusions based on the CI regimen HPHC data. Importantly, the applicant did not include details concerning the uncertainty associated with the reference toxicity values, specifically how they pertain to the potency, effect level, or magnitude of individual HPHC contributions to the total risk or hazard. In particular, the applicant likely overestimated the impact of tobacco-specific nitrosamine (TSNA) reductions in reducing overall cancer risk, in part by extending the NNN cancer reference value to N-nitrosoanabasine (NAB), which is likely less carcinogenic than NNN (Edwards et al., 2017). While the concept of extending the same reference value to another HPHC could be a conservative approach, in this case NAB was lower, meaning that in the aggregate, the applicant's estimated risk due to NAB may have inappropriately contributed to an overestimation of potential total cancer risk reductions. Nonetheless, from a toxicology perspective, the combined hazards and risks are likely similar.

d. Evaluation of literature review

The applicant submitted information detailing a comprehensive literature search (performed by (b)(4) (b)(4)) to identify all possible publications that relate to VLN™ or VLNC cigarettes from 1960 through May 2018. The databases included in the search were Medline, Embase, Biological Abstracts (BIOSIS), Chemical Abstracts, and ToxCenter. Overall, the toxicology review noted that the broad methodology and systematic approach appears to be sufficient for identifying key nonclinical and clinical studies that may be pertinent to the toxicology evaluation of VLN™ cigarettes.

e. Evaluation of nonclinical studies

The applicant submitted summarizing details of eight nonclinical studies, including one that used SPECTRUM® research cigarettes[13] and seven that used QUEST cigarettes. Although QUEST cigarettes, as stated by the applicant, contain VLNC tobacco, virtually every other parameter, including the tobacco

[8] Tobacco Control Act section 911(g)(2)(B)(ii): "[T]he product as actually used by consumers will not expose them to higher levels of other harmful substances compared to the similar types of tobacco products then on the market unless such increases are minimal and the reasonably likely overall impact of use of the product remains a substantial and measurable reduction in overall morbidity and mortality among individual tobacco users."

blend, design features, and HPHCs, is different. As such, it is unclear how the data in the seven associated studies can be extrapolated to the VLN™ cigarettes.

The applicant also cites one study that used SPECTRUM® research cigarettes (Naik, Sajja, Prasad, & Cucullo, 2015). The overall conclusion by the study authors was that the toxicity of the SPECTRUM® cigarettes was equivalent to that of 3R4F cigarettes. This conclusion reached by the authors, that oxidative damage to cells and tissues is not different, is consistent with FDA's evaluation that finds that the overall health risks and hazards are likely similar or lower in the VLN™ cigarettes versus the comparison products selected by the applicant.

f. Summary and conclusion

The applicant states that the health risk profile for the VLN™ cigarettes is the same as that for NNC cigarettes with the only difference being the low nicotine levels in the VLN™ cigarettes. Below I summarize toxicology's key findings:

- Toxicology's evaluation assumed the proposed MRTPs and comparator cigarettes would be used in the same way. This is a conservative approach, given that clinical studies indicate a reduction in CPD for smokers who predominantly use the proposed MRTPs.

- Toxicology conducted a qualitative HPHC evaluation, based on ISO and CI regimens for assessing mainstream smoke. Findings indicate that although there are likely higher exposures to some specific constituents, these higher levels do not appear to impact the overall relative product risks and hazards, given that other constituents associated with similar adverse health outcomes are lower in the VLN™ products compared to conventional cigarettes. Thus, the overall health risks and hazards are likely similar or lower in the VLN™ cigarettes (on a per cigarette basis) versus the comparison products selected by the applicant.

- Toxicology evaluated the applicant's QRA. The ISO regimen HPHC data and associated HPHC evaluation discussed in this review tend to support the applicant's QRA conclusions, which are that noncancer hazards and cancer risks are likely similar or lower for users of VLN™ cigarettes compared to those for users of the comparison products. The CI regimen HPHC data and the associated HPHC evaluation likely demonstrate that the noncancer hazards and cancer risks are similar, but the applicant did not submit a separate QRA to support any health risk-related conclusions based on the CI regimen HPHC data. Nonetheless, the overall toxicant risk to users is likely similar or lower than the toxicant risk for users of the six comparator cigarettes currently on the market.

- The applicant conducted a literature review, and FDA identified one relevant nonclinical study of SPECTRUM VLN™ cigarettes (Naik et al., 2015). This study found that the toxicity of the SPECTRUM® cigarettes was equivalent to that of 3R4F cigarettes. These results are consistent with toxicology's other findings.

- In conclusion, net HPHC exposure from VLN™ cigarettes is similar or lower relative to the comparison products selected by the applicant. While some individual HPHC yields from VLN™ cigarettes are higher relative to the comparison products, the net effect of HPHC changes, specifically the net impact of the lower HPHC yields, translates to similar or lower risks in using

VLN™ cigarettes relative to the comparison products and therefore conventional cigarettes more broadly.

As TPL, I agree with the toxicology review findings. This information provides support for the finding under 911(g)(2)(B)(ii) that "the product as actually used by consumers will not expose them to higher levels of other harmful substances compared to the similar types of tobacco products then on the market unless such increases are minimal and the reasonably likely overall impact of use of the product remains a substantial and measurable reduction in overall morbidity and mortality among individual tobacco users". After consideration of all the toxicological data presented, the overall toxicological risks of VLN™ cigarettes are likely similar to those associated with use of the six comparator products that represent a significant portion of the cigarette market, if used in the same way. The net impact of the lower HPHC yields, translates to similar or lower risks in using VLN™ cigarettes relative to comparison products or conventional cigarettes; therefore, from a toxicological perspective, there would also be the potential for a relative benefit compared to NNC cigarettes for. smokers who switch completely to VLN™ cigarettes; use VLN™ cigarettes to reduce their NNC cigarette use; and/or use VLN™ cigarettes to totally quit smoking.

Clinical Assessment: Biomarkers of Exposure

In this section, we review clinical studies from the applicant and the literature to examine BOEs resulting from using the proposed MRTPs. We also describe findings from one study in the literature examining biomarkers of potential harm (BOPH). More detailed description and analysis can be found in the medical, epidemiology, and BCP reviews.

a. Nicotine BOE

BCP evaluated BOE data, as the applicant provided both a 6-week switching study with BOE outcomes and a review of the VLNC cigarette clinical study literature relevant to BOE.

In the 6-week switching study the BOE outcomes included urinary NNAL (an NNK biomarker), NNN, 3-HPMA (an acrolein biomarker), S-PMA (a benzene biomarker), 1-HOP (hydroxypyrene biomarker), TNE, COHb, and plasma cotinine. Assessments indicated significant decreases from baseline in total nicotine equivalents (TNE) and almost all other measured BOE in both VLN™ King and Menthol King cigarette smokers by Week 6 after switching from UB-NNC cigarettes (decreases in S-PMA and COHb at Week 6 compared to baseline were not significant in the VLN™ King).

Exclusive use of the proposed MRTPs

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 UB-NNC cigarettes. Similarly, Kamens et al. (2019) found that plasma nicotine levels were reduced by 94% in adult smokers following *ad libitum* use of one SPECTRUM non-menthol VLNC cigarette compared to smoking a UB-NNC cigarette. A study from the literature using SPECTRUM VLNC cigarettes found that when consumers exclusively switched to smoking VLNC cigarettes and had no access to other tobacco products for five days, there was a 94% reduction in urinary TNE compared to baseline measurements of participants' UB-NNC cigarettes (Denlinger et al., 2016). **These data support**

that use of VLN™ cigarettes instead of conventional cigarettes can lead to an approximate 95% reduction in exposure to nicotine in smokers, providing additional support for Claim #1 ("95% less nicotine"). This evidence demonstrates that Claim #1 is substantiated, whether "95% less nicotine" refers to the product itself containing 95% less nicotine (see Section III(B)(1) of this review), or to the fact that users would be exposed to 95% less nicotine if they use it to completely replace their use of conventional cigarettes. The only meaning of the claim that wouldn't be substantiated is one that implies a 95% reduction in nicotine exposure during concomitant use with other nicotine containing products. However, this does not raise concerns because such an interpretation is unlikely. See related discussion in the Social Science review regarding whether consumers would understand the extent of their nicotine reduction from dual using VLN™ with other tobacco or nicotine products. In their review, Social Science evaluated the possibility that smokers may incorrectly believe that, by using VLN™, they would reduce their nicotine consumption by 95% even if they kept smoking their usual brand cigarettes in addition to smoking VLN™. The applicant's qualitative consumer research allowed participants to speak about their interpretations of the proposed claims, and participants' statements suggested that they generally understood that "95% less nicotine" refers to the nicotine content of VLN™ cigarettes themselves, rather than users' overall nicotine consumption, which would also depend on their use of other nicotine-containing products (see Section 4.1 of the Social Science review for additional details). We would also like to note that the "95% less nicotine" refers specifically to the *content* of VLN™ cigarettes themselves; whereas the dual use findings of reduced nicotine are about overall exposure; which, although not reduced by 95% in a dual use scenario, still provides substantially reduced nicotine exposure varying by the type, duration, and frequency of other products used. These findings support the finding under 911(g)(2)(B)(i) that "the magnitude of the overall reductions in exposure to the substance or substances 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 or substances". Therefore, these findings support substantiation, understanding, and interpretation among consumers that Claim #1 ("95% less nicotine") refers to the nicotine content of VLN™ cigarettes themselves, rather than users' overall nicotine consumption. **Additionally, these findings provide support that using the proposed MRTPs reduce nicotine consumption, providing support for Claims #2 ("helps reduce your nicotine consumption") and #3 ("... greatly reduces your nicotine consumption").**

Dual use of the proposed MRTPs with other tobacco and nicotine products

Studies from the literature review note that non-compliance with exclusive VLNC cigarette smoking is observed in most participants (76-78%). Most participants instructed to switch completely to VLNCs still use non-study cigarettes (approximately 1-2 CPD). If smokers dual use VLNC and UB-NNC cigarettes but primarily smoke VLNC cigarettes, studies suggest that smokers would still be exposed to lower nicotine levels than they would from smoking just UB-NNC cigarettes, would likely reduce their overall CPD, and would be reasonably likely to experience the effects of reduced dependence on nicotine. Alternatively, participants who dual use VLNC and UB-NNC cigarettes but primarily smoke their UB-NNC cigarettes would have similar nicotine exposure as those who smoke the same number of only UB-NNC cigarettes. Therefore, dual use would not expose smokers to nicotine levels greater than smoking only UB-NNC cigarettes.

Additionally, satisfaction is a predictor of compliance (Nardone et al., 2016), and studies, including the applicant's abuse liability study on VLN™ King cigarettes, find that VLNC cigarettes have lower abuse liability and are not as satisfying as UB-NNC/NNC cigarettes. Consumers who intend to use VLN™

cigarettes for the benefits of reduced nicotine exposure may dually use and smoke VLN™ cigarettes with UB-NNC cigarettes or other nicotine containing products. However, should this occur, studies still support a significant reduction in nicotine exposure compared to smoking UB-NNC/NNC cigarettes. Should participants smoke more UB-NNC than VLNC cigarettes, studies do not suggest that overall nicotine exposure would increase beyond what consumers would be exposed to if they only smoked their UB-NNC cigarettes.

Higher rates of dual ENDS and VLNC cigarette use have been reported in VLNC cigarette smokers compared to NNC cigarette smokers. Nicotine exposure is still reduced compared to UB-NNC cigarettes in participants who dual use VLNC cigarettes with NRT or non-combusted tobacco products (i.e., smokeless tobacco, snus, ENDS).

As such, dual use of VLN™ cigarettes with other tobacco or nicotine-containing products (e.g., UB-NNC cigarettes, ENDS, NRT) is likely to occur in the open marketplace. When considering the range of non-study cigarette use across the sample of participants assigned to smoke VLN™ cigarettes (i.e., the number of UB cigarettes smoked during the course of the study in addition to VLN™ cigarettes), the applicant's 6-week actual use study found that urinary TNE was reduced by averages of 48% and 58% in participants who switched from UB-NNC cigarettes to VLN™ King and Menthol King cigarettes, respectively. Findings from the literature indicate that after 6 and 20 weeks of smoking VLNC cigarettes, accounting for non-compliance, urinary TNE was reduced by an average of 59-60% in participants who switched from UB-NNC cigarettes (Hatsukami et al., 2018; Nardone et al., 2016).

Therefore, as consumers dual use the product (i.e., occasional dual use with UB-NNC cigarettes or other tobacco or nicotine-containing products), nicotine exposure is still substantially reduced in consumers who dual use VLN™ cigarettes with UB-NNC cigarettes or other tobacco or nicotine-containing products (e.g., NRT, ENDS). **These findings provide additional support that using the proposed MRTPs, even along with UB-NNC cigarettes, reduce nicotine consumption, providing support for Claims #2 ("helps reduce your nicotine consumption") and #3 ("... greatly reduces your nicotine consumption").**

The 22nd Century-sponsored studies do not address BOPH; however, the applicant submitted one published study on the effect on BOPH of switching from conventional cigarettes to VLNC cigarettes (Hatsukami et al., 2019). This study evaluated changes in biomarkers of inflammation and oxidative stress and hematologic parameters. No robust changes were identified between the study groups. No conclusions regarding the short- or long-term health risk of VLN™ cigarettes can be made based on the available BOPH data. Therefore, these findings provide further support for the required determination in 911(g)(2)(A)(iii), which states 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 set forth [section 911(g)(1)]".

A presentation from the 2019 Society for Research on Nicotine and Tobacco (SRNT) Conference reported a secondary analysis on data from the 20-week Hatsukami et al. study to determine if menthol flavoring affected trial outcomes (Denlinger-Apte et al., 2019). These data are interpreted with caution, given that the findings have not been peer-reviewed. Compared to baseline, VLNC menthol cigarette smokers had smaller reductions in TNE compared to non-menthol smokers; TNE was reduced overall in menthol smokers who switched from UB-NNC menthol to VLNC menthol cigarettes. These findings suggest that menthol smokers who switch to VLN™ Menthol King cigarettes would also reduce their nicotine exposure.

b. Non-Nicotine HPHC BOE

Exclusive use

Epidemiology and BCP reviewed the Clinical Study Report on BOE of NNC smokers before, during, and after switching from UB to VLN™ cigarettes for the 6-week study. Epidemiology and BCP also evaluated the BOE results from the Hatsukami et al. (2018), which is a 20-week clinical study that assessed the effects of immediate and gradual reduction in nicotine content of cigarettes compared with NNC smokers. All tests in Hatsukami et al. (2018) and the 6-week study were 2-sided.

Hatsukami et al. (2018) found that those who were in the immediate reduction group had significantly lower levels of CO, 3-HPMA, PheT, total NNAL, CEMA, HMPMA, SPMA, and 2-HPMA compared to NNC smokers. Smokers assigned to immediately switch to VLN™ cigarettes had significant reduction in TNE compared to the control group. Smokers assigned to immediately switch to VLN™ cigarettes also had a significantly lower level of NNAL compared to the control group.

In the applicant's 6-week study, the applicant assessed the within-group comparison of changes of biomarkers from baseline, which generally showed a significant decrease in exposure by Week 6. Epidemiology confirmed that there was a significant decrease in urinary Tneq in smokers who switched to VLN™ cigarettes in both the intent to treat (ITT) and per protocol (PP) populations for the 6-week study compared to the baseline. In the PP population, urinary NNAL and 1-HOP were significantly lower in those who switched to VLN™ cigarettes.

These reductions in BOE were also observed in VLN™ cigarette smokers who did not reduce their CPD, although to a lesser extent than in smokers who did reduce CPD. Smokers who reduce their CPD when switching to VLN™ cigarettes experience the greatest reductions in exposure to non-nicotine HPHCs and reduce exposure to a wider range of HPHCs. Studies indicate that dual use is not anticipated to increase overall exposure to non-nicotine HPHCs compared to exclusive UB-NNC cigarette smoking. These findings also provide support for the required finding under 911(g)(2)(B)(ii) that "the product as actually used by consumers will not expose them to higher levels of other harmful substances compared to the similar types of tobacco products then on the market unless such increases are minimal and the reasonably likely overall impact of use of the product remains a substantial and measurable reduction in overall morbidity and mortality among individual tobacco users".

Dual use of the proposed MRTPs with other tobacco and nicotine products

Studies from the literature review note that non-compliance with exclusive VLNC cigarette smoking is observed in most participants (76-78%). Based on the applicant's 6-week study and the literature, if smokers primarily smoke VLN™ cigarettes and occasionally dual use with UB-NNC cigarettes, smokers would still be exposed to lower levels of some non-nicotine HPHCs compared to exclusively smoking UB-NNC cigarettes; however, it is expected that reductions would be smaller compared to those who completely switch. For example, in one 6-week study (Nardone et al., 2016), NNAL levels for participants were reduced, but not significantly. Lower levels of total NNAL and NNN have also been observed over 8 weeks in participants who used VLNC with non-combusted products compared to NNC cigarettes. Additionally, dual use is not anticipated to increase their overall exposure to non-nicotine HPHCs compared to UB-NNC cigarette smoking.

In the open marketplace, VLN™ cigarettes would not be free to consumers as they are in research studies, and this may impact the rate of VLN™ King and VLN™ Menthol King cigarette smoking compared to UB-NNC cigarettes.

c. Summary and conclusion

Below I summarize key BCP and epidemiology findings related to nicotine and non-nicotine biomarkers of exposure:

- Abuse liability studies from the applicant and the literature find that BOEs indicate nicotine exposure is reduced by about 95% with exclusive use of VLN™ or VLNC cigarettes. This provides support for one meaning of Claim #1 ("95% less nicotine")—that using the proposed MRTPs is associated with a 95% reduction in nicotine exposure. It also provides support for Claims #2 and 3 regarding reduced nicotine consumption. In the applicant's 6-week actual use study and the 20-week study, noncompliance was high—most smokers (76-78%) used about 1-2 CPD of UB-NNC cigarettes (Hatsukami et al., 2018). Among these dual users of the VLN™ or VLNC cigarettes and NNC cigarettes, nicotine BOEs are still reduced by at least half.

- Additionally, the BOE results of the applicant's 6-week study and the 20-week study (Hatsukami et al., 2018) demonstrated significant reductions in some other non-nicotine HPHCs among smokers who were instructed to switch to VLNC or VLN™ cigarettes compared to NNC smokers. This was the case even for smokers who did not reduce their CPD.

- The applicant provided limited information about BOPH. While decreases in BOE were found, the extent to which these decreases affect clinical outcomes cannot be determined from the clinical studies. Therefore, based on the available BOPH data, no conclusions can be drawn about the long-term health effects associated with VLN™ cigarette use.

As TPL, I agree with the BCP and epidemiology findings. Based on the available data, exclusive use of the product results in about a 95% reduction in nicotine exposure, and even dual use of the product with NNC cigarettes results in a reduction in nicotine consumption. This provides support for Claims #1-3 and for the required finding in section 911(g)(2)(B)(i) of the FD&C Act. Additionally, using the proposed VLNCs is associated with a reduction in several non-nicotine BOEs, even among smokers who did not reduce their CPD. This provides support for the required finding in section 911(g)(2)(B)(ii) of the FD&C Act that the product as actually used by consumers will not expose them to higher levels of other harmful substances compared to the similar types of tobacco products.

3. Assessment of Potential Health Risks to Individual Tobacco Users and Non-Users

In this section, the evidence from the clinical findings is integrated to assess the potential health risks of use of VLN™ cigarettes among current tobacco users and non-users. Specifically, this section discusses VLN™ cigarettes': (a) dependence and abuse liability, (b) CPD reductions with complete switching, (c) CPD reductions and dual use, (d) adverse health effects from switching, (e) health risks compared to tobacco cessation, (f) health risks to nonusers, and (g) misuse. This information is from BCP, medical, and epidemiology discipline reviews.

The health impact of reducing CPD based on epidemiological studies is discussed in Section III(D)(1)(b).

a. VLN™ Cigarettes' Use Patterns, Abuse Liability and User Dependence

Below I summarize key findings related to VLN™ cigarette's smoking topography, abuse liability, and user dependence. These findings are detailed in the BCP review and are also discussed in the PMTA TPL review:

- Based on the applicant's studies and the literature, individuals who smoke VLNC cigarettes either demonstrate no significant differences in smoking topography relative to those who smoke UB-NNC or NNC cigarettes, or they demonstrate changes in smoking topography measures that are associated with reductions in tobacco smoke exposure (e.g., lower total puff volume). Lack of compensatory smoking behavior was biochemically confirmed through exhaled CO measurements, which indicate no significant differences in CO boost between smoking VLNC and UB-NNC cigarettes. Smokers also do not compensate by increasing their overall CPD when switching to VLNC cigarettes.

- VLN™ King and VLN™ Menthol King cigarettes are associated with reduced abuse liability compared to UB-NNC cigarettes. This conclusion is collectively supported by actual use data in healthy adult smokers after *ad libitum* and controlled VLN™ cigarette smoking and findings from the applicant's literature review on VLNC cigarettes that show lower plasma nicotine and lower positive subjective effects ratings compared to UB-NNC cigarettes. The abuse liability of VLN™ cigarettes is comparable to NRT gum.

- The literature suggests that use of VLNC cigarettes for an extended duration of time is reasonably likely to lead to significant reductions in CPD and decreased dependence scores among smokers interested and not interested in quitting (see Appendix 2 of the BCP review).

- 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). Overall, reducing nicotine exposure can reduce nicotine dependence. This effect is anticipated to lead to long-term reductions in exposure to the smoking-related toxicants associated with morbidity and mortality through reducing smoking and increasing the potential for cessation.

- Among smokers motivated to quit, 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, Donny, Hertsgaard, & Hatsukami, 2015; Hatsukami et al., 2010; Walker et al., 2012). Therefore, the target market for VLN™ cigarettes (i.e., current smokers interested in reducing their nicotine consumption) may have increased adherence with the products compared to participants in the applicant's clinical studies and in the larger VLNC cigarette literature (i.e., current smokers not interested in quitting).

The BCP review concludes that use of **VLN™ cigarettes results in a reduction in nicotine exposure and is reasonably likely to reduce nicotine addiction.**

b. CPD Reductions and Complete Switching from NNC Cigarettes to VLN™ Cigarettes

The health risks of the proposed MRTPs are likely the same compared to continued smoking another brand of cigarette if smoked in the same way. However, the majority of available evidence supports that switching to VLNC cigarettes can lead to an overall reduction in CPD compared to smoking UB-NNC cigarettes (see Appendix 2 of the BCP review). Studies that evaluated CPD across various populations 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 the longest study of VLNC cigarettes to date, total CPD (including study and non-study cigarettes) was reduced by 46-53% in VLNC cigarette smokers compared to NNC cigarette smokers after 20 weeks of use (Hatsukami et al., 2018). When analyzing only the number of VLNC cigarettes smoked during the study, CPD decreased by approximately 57% in VLNC cigarette smokers compared to NNC cigarette smokers. These findings suggest that CPD is likely to gradually decrease the longer smokers use VLN™ cigarettes.

c. CPD and Dual-Using VLN™ Cigarettes with Other Nicotine and Tobacco Products

<u>Dual use with NNC cigarettes</u>

Studies from the literature review note that non-compliance with exclusive VLNC cigarette smoking is observed in most participants (76-78%). If smokers dual use VLNC and UB-NNC cigarettes but primarily smoke VLNC cigarettes, studies suggest that smokers would still likely reduce their overall CPD. The evidence does not suggest that smokers would increase their overall CPD or tobacco product consumption if they dual use VLNC and UB-NNC cigarettes.

The applicant states that the target market for VLN™ cigarettes is current smokers interested in reducing their nicotine consumption. The applicant also acknowledges that the likely situation with VLN™ cigarettes would be one where, upon initiation, consumers who want to quit may have difficulty adhering to just smoking VLN™ cigarettes and may initially alternate between UB-NNC cigarettes and VLN™ cigarettes; however, VLN™/VLNC cigarette studies suggest that the level of dual use with UB-NNC cigarettes is low (two or fewer UB-NNC CPD) and occurs particularly during the early weeks of VLNC cigarette use. As such, dual use with UB-NNC cigarettes would likely subside over time as smokers acclimate to smoking VLN™ cigarettes. The applicant's 6-week actual use study conducted among smokers not interested in quitting found that some VLN™ cigarette smokers initially increased their CPD in the first two weeks of the study, although smoking rates had returned to levels comparable to baseline UB-NNC CPD in these smokers by the end of the study. Because these individuals were more dependent at baseline (based on baseline CPD, smoking history, and Fagerström Test for Cigarette Dependence [FTCD] scores), this effect may be related to level of dependence, where individuals who are more dependent may have greater difficulty reducing CPD. Although in the applicant's study VLN™ CPD were not significantly reduced compared to baseline CPD in all study groups, nicotine exposure was still significantly reduced compared to UB-NNC cigarettes in these smokers.

The applicant's 6-week longitudinal study supports that, as a result of substantially reducing nicotine exposure, switching to VLNC cigarettes can lead to smoking fewer overall cigarettes per day (CPD) compared to ongoing UB-NNC cigarette smoking. These findings are supported by several VLNC

cigarette studies in the published literature, including a 20-week study of VLNC cigarette use among smokers, which is the longest study of VLNC cigarettes to date (Hatsukami et al., 2018). On average, smokers assigned to switch to VLNCs had half the CPD compared to those in the UB-NNC control group. The extent of cigarette reduction depends on the extent of switching to smoking VLN™ cigarettes, although smokers who occasionally smoke UB-NNC cigarettes still experience a significant reduction in CPD compared to smoking UB-NNC cigarettes exclusively. Studies support that as the duration of smoking VLNC cigarettes increases, the reduction in CPD increases. Although results support that participants who dual use VLN™/VLNC cigarettes with their UB-NNC cigarettes still reduce their CPD and that dual use would likely subside over time as smokers acclimate to smoking VLN™/VLNC cigarettes, it is unclear how these findings from clinical studies will generalize to the real-world setting. One possibility is that CPD may be lower in the real-world setting than rates observed in clinical studies, since cigarettes would not be free to consumers as they are in clinical studies. This could be particularly the case as most clinical studies enrolled smokers *not* interested in quitting, and the target market for VLN™ cigarettes (i.e., current smokers interested in reducing their nicotine consumption) may be more motivated to use more VLN™ cigarettes to reduce their nicotine consumption. However, it is also possible that dual use of the proposed MRTPs with NNC cigarettes would be even more prevalent than observed in clinical studies, and CPD reductions would be lower than observed in clinical studies. Satisfaction is a predictor of compliance (Nardone et al., 2016), and studies, including the applicant's abuse liability study on VLN™ King cigarettes, find that VLNC cigarettes have lower abuse liability and are not as satisfying as UB-NNC/NNC cigarettes. Additionally, in the clinical studies reviewed for CPD outcomes, participants were instructed to substitute their UB-NNC cigarettes with VLN™/VLNC cigarettes or to switch completely to smoking VLN™/VLNC cigarettes. Participants were also often incentivized for adherence to the study products. In the open marketplace, consumers will not be incentivized for product adherence and the applicant is not proposing to include conditions of use on the LLA. Given the uncertainty associated with how consumers will use the product and the significant effect of the manner of use on the risk of the product to human health, I recommend that the order include conditions of use on the LLA. Specifically, consumers should receive some type of instruction on how to use VLN™ cigarettes to obtain health benefits, which can occur from switching to VLN™ cigarettes, subsequently reducing their CPD, and ultimately increasing the likelihood that they will be able to quit smoking completely. To address this, I propose that the order require the statement "helps you smoke less" to appear in all LLA that include any of the proposed claims. "Helps you smoke less" directly states how consumers can use VLN™ to potentially achieve a health benefit. In contrast, alternative potential conditions of use such as "switch completely to VLN™" or "use VLN™ exclusively" pose a risk of consumer misunderstanding because completely switching to VLN™ or exclusively using VLN™ are not necessarily sufficient given that smoking VLN™ cigarettes at the same rate as other cigarettes is unlikely to result in a health benefit. Additionally, the applicant tested consumer understanding of labeling that included "helps you smoke less" in its consumer research. This is further detailed in Section III(C)(2) and (4).

<u>Dual use with other nicotine-containing products</u>

Higher rates of dual ENDS and VLNC cigarette use have been reported in VLNC cigarette smokers compared to NNC cigarette smokers. Dual use of VLNC cigarettes with ENDS or NRT may aid in reducing CPD in some individuals (Donny & Jones, 2009; Hatsukami, Hertsgaard, et al., 2013; Hatsukami et al., 2017). Studies do not suggest that dual use of VLNC cigarettes with other tobacco or nicotine-containing products leads to increases in overall CPD or nicotine consumption; nicotine exposure is still reduced compared to UB-NNC cigarettes in participants who dual use VLNC cigarettes with NRT or non-

combusted tobacco products (i.e., smokeless tobacco, snus, ENDS). Among smokers motivated to quit, 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, Donny, Hertsgaard, & Hatsukami, 2015; Hatsukami et al., 2010; Walker et al., 2012).

Different tobacco products potentially have different levels of addiction and toxicity (Sung, Wang, Yao, Lightwood, & Max, 2016). Consumers who use multiple tobacco products "potentially have increased risks of nicotine dependence, adverse health effects, increased exposure to HPHCs, and increased healthcare utilization" (Sung et al., 2016; U.S. Department of Health and Human Services, 2014). The applicant does not address polytobacco use in the MRTPA submission. No information is provided on BOPH, adverse events, or published literature that addresses the health risks of use of VLN™ cigarettes when used with other tobacco products. Nonetheless, given the unique factor is the difference in nicotine, it is likely that the health risks of polytobacco use will not be any different for VLN™ cigarettes compared to NNC cigarettes given the general similarities.

a. Morbidity and Mortality Reductions due to CPD Reductions

Morbidity and mortality reductions that are reasonably likely due to CPD reductions are discussed in detail in our evaluation of population health impact (Section III(D)(1)(b)). Briefly, published epidemiological studies assessing the relationship between smoking reduction and disease risks suggested a potential benefit for some health endpoints such as lung cancer risk in those who reduced CPD by more than 50% compared to non-reducers. Past studies have not consistently demonstrated that a reduction in CPD reduces mortality; however, a recent study that evaluated changes in smoking patterns over a longer period of time than previous studies found that all-cause mortality was lower among smokers who reduced their CPD compared to those who maintained their CPD. The evidence provided by the applicant also suggests that reduced cigarette consumption, rather than complete smoking cessation, is the main benefit of VLN™ cigarettes. However, it is also reasonably likely to infer that VLN would reduce users' nicotine dependence, which in turn could also lead to reduced cigarette consumption, increased quit attempts, and greater likelihood of future smoking cessation.

b. Adverse Health Effects from Switching to VLN™ Cigarettes

Medical reviewers considered the available adverse event and study-related health endpoints from three applicant-sponsored clinical studies as well as adverse event and safety information from two clinical studies in the published literature to evaluate specific issues about the product as detailed below (Donny et al., 2015; Hatsukami et al., 2018). Long-term studies assessing health effects are not available. While there are limited short-term and no long-term studies evaluating health effects of VLN™ cigarettes, the risks for adverse health effects are likely similar as for those associated with NNC cigarettes given that the main difference between the proposed products and NNC cigarettes is the nicotine content. The applicant primarily relies upon two publications, Donny et al. (2015) and Hatsukami et al. (2018), to substantiate the risk profile and safety of VLN™ cigarettes, respectively.

It is expected that VLN™ cigarette users who use the products in the same way as NNC cigarettes will have the same short- and long-term health effects as those that occur with NNC cigarette smoking. Cigarette smoking has well-documented "immediate adverse health consequences" (U.S. Department of Health and Human Services, 2004). For example, respiratory symptoms such as cough, increased sputum production, and wheezing occur shortly after initiation of cigarette smoking (U.S. Department of Health and Human Services, 2004). Respiratory infections such as bronchitis and pneumonia are "more

frequent and severe among smokers" (U.S. Department of Health and Human Services, 2004, 2014). Smoking's short-term effects also include acute cardiovascular events and exacerbation of asthma.

Cigarette smoking also adversely affects long-term health. It is well documented that smoking increases all-cause morbidity and mortality. "Cigarette smoking accelerates the age-related decline in lung function that occurs among never smokers" (U.S. Department of Health and Human Services, 2004). Compared to non-smokers, cigarette smokers have higher risk for many chronic illnesses, such as heart disease, chronic obstructive pulmonary disease, stroke, and peripheral vascular disease. Smokers have a much higher risk for malignant diseases of all organ systems compared to non-smokers (U.S. Department of Health and Human Services, 2004). Many aspects of reproductive health are negatively impacted by smoking.[9]

Among smokers motivated to reduce or eliminate nicotine exposure, the health risks for those who switch to VLN™ cigarettes are likely less harmful than continued NNC cigarette smoking. Smokers who completely switch to VLN™ cigarettes may experience weight gain. If smokers dual use NNC cigarettes with VLN™ cigarettes, then they may experience some weight gain, in addition to the adverse health effects of continued NNC cigarette smoking. However, the BCP review notes (see section on abuse liability) that the likelihood that current tobacco product users would completely switch to VLN™ cigarettes is low. The medical review also notes that this weight gain effect may differ in smokers who are motivated to reduce their nicotine exposure or quit smoking. Smoking increases the risk of CVD and thrombosis. While in vivo and in vitro studies have indicated that VLN™ cigarettes may cause increased platelet activation, compared to other cigarettes with higher nicotine content, an increased risk of thrombosis has not been substantiated based on adverse event reporting in clinical studies.

From available evidence, the adverse health effects caused by VLNCs or VLN™ cigarettes are likely to be similar to traditional cigarettes if smoked the same way. However, given the dramatically lower levels of nicotine in VLN™ cigarettes, switching from conventional cigarettes to the proposed MRTPs is reasonably likely to lead to reduced nicotine dependence, which could result in reduced CPD, and for some, increased likelihood of quitting cigarettes altogether; translating to a substantial and measurable reduction in morbidity and mortality.

c. Health Risks Compared to Tobacco Cessation and Use of FDA-Approved Smoking Cessation Drug or Device Products

The applicant did not provide information comparing the short- and long-term health effects of complete or incomplete VLN™ cigarette switching to abstinence (quitting). As stated above, VLN™ cigarettes are likely to have similar short- and long-term health risks as NNC cigarettes if product use frequency and amount are the same. Abstinence from NNC cigarettes is far preferable because it is associated with substantial health benefits (U.S. Department of Health and Human Services, 2004). Abstinence from all tobacco, including cigarettes, is one of the most important factors in improving individual health. To be balanced, achieving abstinence by going "cold turkey" or using other means such as behavioral methods or pharmacotherapy can have health risks (e.g., nicotine withdrawal

[9] For example, the 2001 Surgeon General's Report lists numerous adverse reproductive effects associated with smoking compared to never smoking: increased perinatal mortality—both stillbirth and neonatal deaths—and the risk for sudden infant death syndrome (SIDS), increased risk of preterm premature rupture of membranes, abruptio placentae, and placenta previa, preterm delivery, and delivery of low birth weight infants.

syndrome, weight gain, depression, cough, mouth ulcers (Rigotti, 2020) but the benefits of abstinence (quitting) far outweigh these risks.

The applicant did not provide clinical data to evaluate the relative health risks of switching to VLN™ cigarettes compared to using approved cessation products. As mentioned above, smokers who switch to VLN™ cigarettes could gain weight from decreased nicotine exposure and, concurrently, have the same adverse consequences of continued smoking. There is no clinical data to support this scenario. Smoking cessation using FDA-approved products is far preferable than smoking any combustible products, including VLN™ cigarettes. FDA-approved smoking cessation products have risks, but these products have known records of safety and efficacy. Though there are risks with abstinence and cessation therapies, the benefits of quitting far outweigh these risks. Lastly, given the lower abuse liability of VLN™ cigarettes, it is not particularly likely that VLN™ cigarettes would deter smokers from abstinence with or without FDA-approved smoking cessation products. The applicant did not provide information on abstinence and did not address the issue of deterrence from FDA-approved smoking cessation therapies. While it is optimal for smokers who are interested in quitting to directly switch to FDA-approved cessation therapies or quit without therapy, it is well established that smoking cessation is difficult and that many are not able to successfully convert. For some individuals, VLNC cigarettes can serve as an interim transition to reduce nicotine dependence levels and cut down smoking, which may aid in future quit attempts. VLNC cigarettes are less reinforcing than NNC cigarettes and the likelihood of long-term use of VLNC cigarettes is lower than NNC cigarette use.

d. Health Risks to Non-Users

The applicant did not submit product-specific information related to the effect of VLN™ cigarettes on non-users, but it anticipates that this effect would be similar to NNC cigarettes. FDA agrees with the applicant. The most important health risk to non-users from any combusted product is involuntary exposure to secondhand smoke (SHS) and thirdhand smoke (THS). Because VLN™ cigarettes are combusted tobacco products, it is expected that similar health effects will occur when non-smoking bystanders are exposed to SHS and THS from VLN™ cigarettes™. In the event that a smoker exposing a non-user to SHS and THS reduces their CPD when using VLN™ cigarettes, a reduction in non-user exposure to SHS and THS would be expected.

e. Misuse

The applicant did not submit information on potential misuse or malfunction of the VLN™ cigarettes. The applicant states that these products perform like NNC cigarettes and will be used in the same manner. The medical review does not expect any different human factor issues to arise with VLN™ cigarettes because these cigarettes have no unique use characteristics that differ from NNC cigarettes. As discussed in the medical review, the human factors issues related to cigarettes leading to misuse or injury are well known: (1) improper storage, allowing access to unused products by children; (2) improper disposal of butts (i.e., “butt waste”) that when ingested may be hazardous to the health of small children and animals (Novotny et al., 2011); and (3) incomplete extinguishment of lighted cigarette products leading to fires causing personal injury—the leading cause of fire deaths in the U.S.—and property damage (Leistikow et al., 2000). Thus, there are not any different human factors issues expected to arise with VLN™ cigarettes because they have no unique use characteristics that differ from NNC cigarettes.

f. Summary and conclusion

FDA's assessment of potential health risks to individual tobacco users and nonusers from clinical studies is summarized as follows:

- VLN™ King and VLN™ Menthol King cigarettes are associated with reduced abuse liability compared to UB-NNC cigarettes. There is consistent evidence in the literature suggesting that use of VLNC cigarettes for an extended duration of time is associated with significantly decreased dependence scores among smokers interested and not interested in quitting. Among smokers motivated to quit, 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. Thus, VLN™ cigarettes are reasonably likely to reduce nicotine addiction, contributing to a reduction in morbidity and mortality.

- The majority of available evidence supports that switching to VLNC cigarettes can lead to an overall reduction in CPD compared to smoking UB-NNC cigarettes. Reductions have ranged from 11% to 46% in 6-week clinical studies. In the longest clinical study (20 weeks), total CPD in the group assigned to smoke VLNC cigarettes was about 50% of that of the NNC cigarette control group. However, most smokers instructed to use VLNC exclusively in clinical studies still use a few NNC cigarettes (two or less per day). Still, smokers who use predominantly VLN™ cigarettes significantly reduce their CPD, though to a lesser extent than smokers who switch completely. Reductions in morbidity and mortality that are reasonably likely due to these reductions in CPD are discussed in Section III(D)(1)(b).

- Higher rates of dual ENDS and VLNC cigarette use have been reported in VLNC cigarette smokers compared to NNC cigarette smokers. Smokers who use VLNC along with ENDS or NRT may further reduce their CPD. Among smokers motivated to quit, 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.

- Uncertainty remains about how clinical study findings will generalize to the real-world setting. CPD reductions may be even greater as cigarettes would not be free to be consumers (as they are in clinical settings) and users may be smokers who are motivated to reduce their CPD (clinical studies only include smokers who do not intend to quit). CPD reductions may be lower, as studies have found smokers do not find VLNCs satisfying, and satisfaction predicts product uptake. CPD reductions also may be lower in the absence of instructions to use the product exclusively (as participants were given in clinical studies).

- If smoked the same way, it is expected that VLN™ cigarette users will generally have the same negative short- and long-term health effects as those that occur with NNC cigarette smoking. The likelihood and extent to which smokers and nonsmokers (who are exposed to SHS and THS) experience risk reductions depend on the extent of the smokers' CPD reduction.

- Among smokers motivated to reduce or eliminate nicotine exposure, the health risks for those who switch to VLN™ cigarettes are likely less harmful than continued NNC cigarette smoking. Smokers who completely switch to VLN™ cigarettes may experience weight gain. If smokers dual use NNC cigarettes with VLN™ cigarettes, then they may experience some weight gain, in

addition to the adverse health effects of continued NNC cigarette smoking; however, decreases in NNC cigarette smoking will also likely decrease overall health risks.

- The applicant did not provide information comparing the short- and long-term health effects of complete or incomplete VLN™ cigarette switching to abstinence or to using approved cessation products.

- The applicant did not submit information on potential misuse or malfunction of the VLN™ cigarettes. The medical reviewer does not expect any different human factors issues to arise with VLN™ cigarettes because these cigarettes have no unique use characteristics that differ from NNC cigarettes.

As TPL, I agree with these findings. If used in the same way, the health risks of using the proposed MRTPs are the same as NNC cigarettes, and the proposed MRTPs do not raise additional concerns regarding misuse and health effects compared to NNC cigarettes. However, the available evidence suggests the proposed MRTPs have reduced abuse liability and smokers who use them gradually reduce their CPD. Although a significant reduction in tobacco-related death and disease has not been demonstrated, I find that it is reasonably likely that switching to the proposed MRTPs would lead to a substantial and measurable reduction in death and disease through reduced nicotine dependence, cutting down on cigarettes, and for some, increasing the likelihood of quitting cigarettes altogether.

C. Consumer Understanding and Perceptions

Social science evaluated whether the proposed LLA would enable consumers to understand the proposed modified risk information and its significance in the context of total health, and whether the proposed labeling and marketing would mislead consumers about the demonstrated harms or disease risks of using the proposed MRTPs. See sections 911(h) and 911(g)(2)(B)(iii). This includes assessing whether consumers would understand (1) the nicotine content of the proposed MRTPs, (2) the conditions of use of the proposed MRTPs, (3) the addiction risks, and (4) the health risks other than addiction. This evaluation was informed by the applicant's quantitative study of the product's labeling with the proposed Claims #1-3 and the disclaimer, and four qualitative studies of different versions of the product's labeling with proposed Claims #1-3 and other FDA-identified claims. The evaluation was also informed by peer-reviewed literature. I find that the totality of evidence on consumer understanding supports that if the LLA include the statement "helps you smoke less," the LLA will enable consumers to understand the proposed modified risk information and will not mislead consumers into holding inaccurate beliefs about the products' health risks or harms or the definitiveness of the evidence regarding the products' relative risks or harms.

1. Understanding of Nicotine Content

Regarding whether consumers would comprehend the explicit meaning of the proposed statements about reduced nicotine, social science examined the claims themselves, the applicant's research on consumer responses to the claims, and previously published research on consumer responses to statements with wording similar to the wording in the proposed claims. We found that the claims are relatively simple and concrete (including the statement of "95% less"), and that each instance of LLA includes multiple statements reinforcing the main idea of substantially reduced nicotine. The statements

include a numeric description (“95% LESS NICOTINE”) as well as a verbal qualifier (“greatly reduces”) to convey the extent of the nicotine reduction, which may be helpful for consumers with lower levels of numeracy. The disclaimer “Nicotine is addictive. Less nicotine does **NOT** mean safer. All cigarettes can cause disease and death.” begins with a statement about nicotine being addictive, which gives additional context regarding the meaning of statements about reduced nicotine. The applicant submitted four phases of qualitative research examining consumer comprehension of the applicant-proposed claims’ explicit meaning as well as various other claims with different characteristics. These studies found support for using the “95% less” wording because it was brief and made clear that the reduction in nicotine was substantial. Other claims the applicant tested (e.g., “5% of the nicotine”) were misunderstood. In the applicant’s quantitative research, most participants spontaneously brought up the low nicotine content when asked for an open-ended response about how they would describe the product to a friend or family member (65%, 66%, and 67% of current, never, and former smokers, respectively), although the applicant did not submit any information to FDA about its methodology for analyzing or coding these open-ended responses. Previously published research also tested consumer comprehension of reduced nicotine claims with various phrasing, finding that the inclusion of a percentage reduction (i.e., 95%) helped participants grasp the extent of the nicotine reduction (Byron, Hall, King, Ribisl, & Brewer, 2019).

Lastly, social science considered whether consumers would understand the extent of their nicotine reduction from dual-using VLN™ with other tobacco or nicotine products. In particular, social science evaluated the possibility that smokers may incorrectly believe that, by using VLN™, they would reduce their nicotine consumption by 95% even if they kept smoking their usual brand cigarettes in addition to smoking VLN™. The applicant’s qualitative and quantitative consumer research did not directly address this question, nor could we find studies in the published literature directly addressing this question. However, the applicant’s qualitative consumer research allowed participants to speak about their interpretations of the proposed claims, and participants’ statements suggested that they generally understood that “95% less nicotine” refers to the nicotine content of VLN™ cigarettes themselves, rather than users’ overall nicotine consumption, which would also depend on their use of other nicotine-containing products. For example, participants stated, “It’s saying exactly what it is. It’s 95 percent less nicotine and because of that you’re not consuming the amount normally,” and, “It has less nicotine in it, therefore it absolutely would give you less nicotine consumption” (see Appendix in Section 9 of the social science review). Among participants who smoked heavily, one of their main concerns with using VLN™ was that they “want their nicotine” and “might smoke more cigarettes to get the same amount of nicotine,” suggesting that they understood that their cumulative nicotine exposure depends on their overall level of use of nicotine-containing products. Also, consistent with the idea that consumers will understand “95% less nicotine” to refer specifically to the content of VLN™ cigarettes themselves, FDA maintains requirements for relative nutrient content claims on food labeling (e.g., “65% less fat than regular potato chips”), and these claims refer to products’ contents without reference to potential consumption of other products containing the same nutrients (see Appendix B in Institute of Medicine, 2010). Altogether, we believe smokers would understand that their total nicotine consumption will not be reduced by 95% if they dual use VLN™ with other nicotine-containing products.

Taken together, these findings suggest that the proposed LLA would indeed enable most consumers to comprehend the claims’ explicit meaning that VLN™ cigarettes contain much lower levels of nicotine than other cigarettes.

2. Understanding of Conditions of Use

Regarding conditions of use, social science examined whether consumers would understand that VLN™ cigarettes can help smokers reduce their smoking frequency or duration, which can reduce their exposure to nicotine and other HPHCs and potentially their disease risk. Reviewers found that the proposed LLA include no information on conditions of use, such as how consumers should use VLN™ to reduce their exposure to HPHCs and potentially disease risk. In qualitative in-depth interviews, some of the participants did not appear to understand the conditions of use: after viewing VLN™ cigarette packs with the proposed modified risk labeling, they did not understand the need to cut down or stop smoking in order to benefit from VLN™ cigarettes. In contrast, participants appeared to understand this better after viewing alternative packs that included the proposed claims plus an additional statement, "Helps you smoke less," based on the applicant's study reports and social science's evaluation of a random sample of transcripts from the Phase 4 qualitative study. Participants found that this statement was "simple" and "to-the-point" and "uses verbiage that is easily understood."

The applicant's quantitative consumer research did not include items assessing whether the proposed LLA would enable consumers to understand the conditions of using VLN™ cigarettes, such as items asking about how much smokers would have to cut down on their cigarette smoking (e.g., cigarettes per day or number of days smoked) in order to reduce their HPHC exposure and potentially disease risk using VLN™ cigarettes. This was also the case for a study condition testing a different version of the labeling that the applicant did not propose to use; this version specifies the conditions for use that could lead to a benefit for consumers ("Helps you smoke less").

Among smokers who reported an intention to purchase VLN™ cigarettes, the quantitative study did ask about how their purchase of VLN™ cigarettes would affect their purchases of other tobacco products, finding that most smokers reported that VLN™ cigarettes would replace at least some of their current purchases of other cigarettes. However, it was unclear whether smokers intended to use VLN™ cigarettes to cut down on their overall cigarette consumption or simply replace all or some of their current cigarette. Given these findings, it appears that instructions to convey how to use VLN™ cigarettes would benefit consumers. Appropriate statements to convey how the product should be used to obtain a benefit were considered, including detailed and explicit instructions about switching completely and reducing cigarette consumption; however, these types of explicit statements were not tested relative to improved understanding. Since the applicant qualitatively tested "helps you smoke less", as instructions for use that demonstrated improved understanding for conditions to use the product to obtain the intended benefit, I recommend that the order require that VLN™ cigarettes' LLA include "Helps you smoke less," as this statement is necessary to enable consumers to understand the manner in which they must use the product in order to obtain a benefit.

3. Understanding of Addiction Risk

Social science posited that, if the proposed LLA enable people to understand the modified risk information in the context of total health, people will perceive VLN™ cigarettes as less addictive than other cigarettes and other nicotine-containing tobacco products (e.g., e-cigarettes and snuff) and similarly addictive as NRT. This is based on other FDA disciplinary reviews finding that VLN™ cigarettes' abuse liability is substantially lower than that of other cigarettes and similar to that of NRT, and it is reasonably likely that smokers can use VLN™ cigarettes to reduce their nicotine dependence over time (see the BCP review).

To examine whether the proposed LLA will enable consumers to understand the addiction risks of VLN™ cigarettes, the applicant conducted a quantitative study in which participants were randomly assigned to view either images of a VLN™ cigarette pack or a Marlboro Gold™ cigarette pack (total sample size n=29,219; Protocol #: 5180080-VLN™-B2). The VLN™ cigarette pack either contained the proposed modified risk information or an alternative version of the information. Participants were also shown a brief description of VLN™ cigarettes that included modified risk information (see Figure 3 in the social science review). After viewing the cigarette pack images, participants reported their perceptions of the addictiveness of VLN™ cigarettes or Marlboro Gold™ cigarettes. Participants were also randomized to report their perceptions of health risk from using either conventional cigarettes in general (providing the brand examples of Marlboro, Camel, Newport, and Winston), snuff, e-cigarettes, or NRT.

Findings suggest that the proposed LLA would enable consumers to understand the addiction risks of smoking VLN™ cigarettes. Consistent with VLN™'s very low nicotine level, participants perceived VLN™ cigarettes as substantially less addictive than other cigarettes after viewing the VLN™ pack image with the proposed modified risk claims and the alternative versions of the information. At the same time, participants still perceived some risk of addiction from smoking VLN™ cigarettes, placing them in a similar range as NRT (*M*s = 3-4 on a 5-point scale). In an absolute sense, we expect that these ratings of addiction risk from VLN™ and NRT may reflect overestimates of abuse liability and dependence potential (which appear low; see the BCP review and, e.g., West et al., 2000), which could discourage use of VLN™ among people who are not already addicted to smoking cigarettes. The above findings held across current, former, and never smokers, and are consistent with prior research finding that most U.S. adults believe that nicotine is the main addictive substance in tobacco (O'Brien et al., 2017).

As an example, adult current smokers had addiction risk perceptions that were lower for VLN™ cigarettes than for either Marlboro Gold™ or conventional cigarettes in general. Perceptions of addiction risk for VLN™ cigarettes were also lower than those for snuff and e-cigarettes and higher than those for NRT. These findings were also observed among former smokers. Among young adult never smokers, perceptions of addiction risk for VLN™ cigarettes were generally lower than those for conventional cigarettes, Marlboro Gold™, snuff, and e-cigarettes; however, perceptions for VLN™ cigarettes were not significantly different from those for NRT.

4. Understanding of Health Risks, other than Addiction

Social science posited that, if the proposed LLA enable people to understand the modified risk information, people will perceive VLN™ cigarettes as posing health risks that are (a) moderate or high, (b) higher than NRT, (c) similar to other cigarettes when smoked in the same way (i.e., same frequency

and duration), and (d) lower than other cigarettes when used to reduce one's smoking.[10] As the applicant states, based on a toxicological risk assessment, VLN™ cigarettes "are not considered to be less hazardous than conventional cigarettes" (Executive Summary, pp. 18-20), but their use may lead to a population health benefit through reductions in smokers' dependence on cigarettes.

Social science evaluated the M/A/R/C Quantitative Study to make this assessment. In this study, participants rated the health risks of using VLN™ cigarettes, Marlboro Gold™ cigarettes, and other tobacco and nicotine products (total sample size n=29,219; Protocol #: 5180080-VLN™-B2). Before rating the health risks of smoking VLN™ cigarettes, participants were shown VLN™ packs containing either the proposed modified risk information or alternative versions of the information. Participants were then asked, "Taking into consideration everything you know about [product], indicate what you believe is the risk of the following long-term or lifetime health-related issues" because of smoking VLN™ and using other products. The 18 health-related issues were: lung cancer, mouth/ throat cancer, heart disease, emphysema, earlier death, respiratory infections, 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.

Supporting (a), the applicant's research found that participants indeed perceived VLN™ as presenting risks of tobacco-related diseases that were moderate to high (mean ratings between 3 and 4 on a 5-point scale). Supporting (b), participants perceived VLN™ cigarettes' risks as significantly higher than the risks posed by NRT. These findings on absolute risk perceptions of VLN™ and risk perceptions of VLN™ compared to NRT appear consistent with accurate consumer understanding of the proposed modified risk information and its significance in the context of total health.

However, regarding (c) and (d), the applicant's quantitative research found that, after viewing VLN™ packs with the proposed modified risk information, participants perceived VLN™ cigarettes as presenting lower risks of tobacco-related diseases -- including lung cancer, mouth/throat cancer, heart disease, and 15 other tobacco-related diseases and health effects – compared to other cigarettes. However, in this research, the survey questions had limitations in that they did not include information regarding patterns or frequency of use, and the research did not assess the assumptions participants made in answering questions related to disease risks. Therefore, it is unclear whether these perceptions reflect consumer misperceptions of toxicity or correct consumer understanding of the reasonably likely reduction in disease risks resulting from using VLN™ cigarettes, which are less addictive, and smoking fewer of them over time. Social science's evaluation of randomly selected transcripts from Phase 4 of the qualitative research found that some participants appeared to believe that VLN™ cigarettes were less toxic than other cigarettes because of the reduced nicotine content, while other participants believed that VLN™ cigarettes were less likely to cause disease because people would be less likely to smoke them long enough to get diseases (see Section 4.2 of the social science review for a more detailed discussion). Still, findings are generally consistent with prior published research that suggests that, without corrective or clarifying information, many U.S. consumers are at risk of misinterpreting statements about reduced nicotine content cigarettes (e.g., "Imagine if tobacco companies were required to remove 95% of the nicotine from cigarettes") to mean that the cigarettes would be less toxic and carcinogenic than other cigarettes (Byron et al., 2019; Bansal-Travers et al., 2010; Borrelli & Novak,

[10] Although the applicant also examined perceptions relative to snuff and e-cigarettes, we do not have data to evaluate the accuracy of consumer understanding of these comparisons.

2007; Byron et al., 2018; Denlinger-Apte et al., 2017; Mutti et al., 2011; O'Brien et al., 2017). Indeed, TPSAC committee members also stated it was unlikely that participants thought through the products' addictiveness (and the corresponding effects on use frequency, duration, and, in turn, disease risks) when rating the risks of smoking VLN™ cigarettes.

Taken together, the published literature and the applicant's findings support that, without additional information, many U.S. consumers, including smokers and non-smokers, would be at risk of misunderstanding the manner in which VLN™ cigarettes must be used in order to obtain a benefit. In light of these findings, it appears that instructions to convey the purpose of the product and how to use it would benefit consumers. Appropriate statements to convey how the product needs to be used to obtain a benefit were considered, including detailed and explicit instructions about switching completely to the product or reducing your cigarette consumption; however, to avoid overly complicated and untested instructions on the LLA without evidence of improved understanding, I am proposing to include "helps you smoke less", which was part of the LLA tested by the applicant, as instructions of how to use the product to obtain the intended benefit. This statement was tested in the applicant's submitted studies and communicates the way the product needs to be used to gain a benefit. Therefore, **I find it necessary to require VLN™ cigarettes' modified risk LLA to include an explicit statement about the manner in which the product must be used in order to obtain a benefit ("Helps you smoke less").** By including this statement in a way that will be noticed and read, the LLA will enable consumers to better understand the significance of the reduced nicotine claims, the relevance to their personal health (or the irrelevance, if the person does not wish to smoke less), and the reason why the manufacturer would be providing the information about nicotine to consumers.

Additionally, if FDA authorizes the applicant to market VLN™ cigarettes as modified risk products, the authorization letter should recommend that the applicant include the disclaimer "Nicotine is addictive. Less nicotine does NOT mean safer…" on VLN™ pack LLA given that it was present on all of the labeling that the applicant tested in its quantitative consumer research, and the letter should also require the applicant to test the disclaimer in a postmarket study. Several aspects of the disclaimer are inconsistent with expert recommendations for disclaimers, and prior research suggests that poorly designed disclaimers can confuse consumers and change their perceptions, attitudes, or decisions in a manner opposite of that intended (Green & Armstrong, 2012). Indeed, in a pre-submission meeting with the applicant, FDA recommended that the applicant conduct a study comparing consumer understanding across participants who did and did not see the disclaimer, to assess the disclaimer's effects on understanding of the modified risk information. However, the applicant submitted no evidence about the disclaimer's effect on consumer understanding. Conducting a postmarket test can provide FDA with evidence about whether the disclaimer helps enable consumers to understand that VLN™ cigarettes present the same disease risks as other cigarettes if smoked in the same way, or whether it confuses people about the health risks of VLN™ cigarettes.

Summary and Conclusion

Social science evaluated whether consumers understood (1) the nicotine content of the proposed MRTPs, (2) the conditions of use of the proposed MRTPs, (3) the addiction risks, and (4) the health risks, other than addiction. Their evaluations were informed by one quantitative study and four qualitative studies submitted by the applicant, in addition to the published literature. Their findings are summarized below:

- (1) The applicant's qualitative research suggested that consumers would understand the claims to mean the nicotine content of VLN™ is substantially lower compared to other cigarettes. In particular, "95% less nicotine" is brief and makes clear that the reduction in nicotine content is substantial. Claims #2 and #3 reinforce this point and provide a verbal qualifier ("greatly reduces") to convey the substantial reduction in nicotine exposure, which may be helpful for consumers with lower levels of numeracy. Qualitative research also suggested that consumers generally understood that "95% less nicotine" refers to the nicotine content of VLN™ cigarettes themselves, rather than users' overall nicotine consumption. Similarly, Claims #4-10 are clear that the statements about nicotine refer to the nicotine content of the cigarettes rather than users' overall nicotine exposure, which is affected by their use of other nicotine-containing products.

- (2) Reviewers found that the proposed LLA include no information on conditions of use, such as how consumers should use VLN™ to reduce their exposure to HPHCs and potentially disease risk. In qualitative research, some participants did not appear to understand the need to cut down or stop smoking in order to benefit from VLN™ cigarettes. Based on the quantitative research, it was unclear whether smokers intended to use VLN™ to cut down on their overall cigarette consumption or simply replace all or some of their current cigarette use with VLN™ cigarettes.

- (3) Findings from the applicant's quantitative study suggest the proposed LLA would enable consumers to understand the addiction risks of smoking VLN™ cigarettes. Consistent with VLN™ cigarettes' very low nicotine level, participants perceived VLN™ cigarettes as substantially less addictive than other cigarettes after viewing the VLN™ pack image with the proposed modified risk claims and the alternative versions of the information. At the same time, participants still perceived some risk of addiction from smoking VLN™ cigarettes, placing them in a similar range as NRT.

- (4) Social science posited that, if the proposed LLA enable people to understand the modified risk information, then people will perceive VLN™ cigarettes as posing health risks that are (a) moderate or high, (b) higher than NRT, (c) similar to other cigarettes when smoked in the same way (e.g., same frequency and duration), and (d) lower than other cigarettes when used to reduce one's smoking. While findings supported (a) and (b), results for (c) and (d) were unclear. Regarding (c) and (d), the applicant's quantitative research found that, after viewing VLN™ cigarette packs with the proposed modified risk information, participants perceived VLN™ cigarettes as presenting lower risks of tobacco-related diseases compared to other cigarettes, including lung cancer, mouth/throat cancer, heart disease, and 15 other tobacco-related diseases and health effects. However, it is challenging to evaluate these findings, given that the survey questions did not include information regarding patterns or frequency of use (i.e., whether VLN™ cigarettes would be used at the same rate or be used to cut down), and the research did not assess the assumptions participants made in answering these questions. Still, findings are generally consistent with prior published research that suggests that, without corrective or clarifying information, many U.S. consumers are at risk of misinterpreting statements about reduced nicotine content cigarettes.

As TPL, I agree with these findings. To address the issue outlined in (2) and (4) above, and in light of these findings, **I recommend that the order require VLN™ cigarettes' modified risk LLA to include an**

explicit statement about the manner in which the product must be used in order to obtain a benefit, "Helps you smoke less". By including this statement in a way that will be noticed and read, the LLA will enable consumers to better understand the significance of the reduced nicotine claims, the relevance to their personal health (or the irrelevance, if the person does not wish to smoke less), and the reason why the manufacturer would be providing the information about nicotine to consumers. This will enable consumers to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health.

Additionally, the authorization letter should recommend that the applicant include the disclaimer "Nicotine is addictive. Less nicotine does NOT mean safer…" on VLN™ pack LLA given that it was present on all of the labeling that the applicant tested in its quantitative consumer research, but the letter should also require the applicant to test the disclaimer in a postmarket study. Several aspects of the disclaimer are inconsistent with expert recommendations for disclaimers, and prior research suggests that poorly designed disclaimers can confuse consumers and change their perceptions, attitudes, or decisions in a manner opposite of that intended (Green & Armstrong, 2012). In a pre-submission meeting with the applicant, FDA recommended that the applicant conduct a study comparing consumer understanding across participants who did and did not see the disclaimer, to assess the disclaimer's effects on understanding of the modified risk information. However, the applicant submitted no evidence about the disclaimer's effect on consumer understanding. Conducting a postmarket test can provide FDA with evidence about whether the disclaimer helps enable consumers to understand that VLN™ cigarettes present the same disease risks as other cigarettes if smoked in the same way, or whether it confuses people about the health risks of VLN™ cigarettes. Thus, **I recommend that the order require the applicant to conduct such a study of the disclaimer as part of postmarket surveillance**; this is discussed further in Section IV(C).

Social science did not specifically evaluate consumer understanding of FDA-identified Claims #4-10 in detail. These statements appear to convey the same information as applicant-identified Claims #1-3. Specifically, the claims are limited to information about VLN™ cigarettes' nicotine content and how it compares with that of other cigarettes, although some of the claims describe the nicotine content in absolute terms (e.g., ".27 mg"), use qualitative comparisons (e.g., "substantially lower"), or include comparators (e.g., "the top 100 cigarette brands"). The applicant's qualitative research on consumer understanding (described below in Section 4; M/A/R/C Qualitative Study) examined participants' responses to claims with alternate phrasing similar to these variations. The one exception is Claim #9, which describes the source of VLN™ cigarettes' reduced nicotine content (i.e., "unique technology and plant breeding expertise" allows the company to grow tobacco with different nicotine levels). This statement is similar to background information about VLN™ cigarettes viewed by participants in the applicant's quantitative consumer perception research (see Sections 4 and 5 below; M/A/R/C Research Quantitative Study). The background information stated: "A new tobacco product called VLN™ (Very Low Nicotine) is currently in development… VLN™ cigarettes are made from a tobacco plant that has been altered to contain much lower levels of nicotine than the tobacco used in traditional cigarettes." Thus, although the applicant did not specifically examine consumer responses to FDA-identified Claims #4-10, any potential concerns are mitigated by the fact that these claims appear to convey the same information as Claims #1-3 and the information that participants viewed in the applicant's quantitative consumer research.

D. Tobacco Use Behavior and Impacts to the Population as a Whole

An assessment of the impact of an MRTP marketing authorization on the population as a whole is primarily a function of the relative health risks of the proposed product and the likelihood of tobacco use behavior change, including due to the modified risk marketing. Assessing the impact to the population as a whole includes an assessment of the potential impact of the product, including with the proposed modified risk information, on tobacco users and non-users if the product were to be authorized as an MRTP.

Several lines of evidence were provided to inform the assessment of the impact of the proposed MRTPs on tobacco users and non-users, including abuse liability studies, pre- and post-market observational studies, and consumer perception studies evaluating the impact of the proposed modified risk claims. In addition, the applicant provided a population model of the potential impact of the proposed MRTPs. A summary of these studies and conclusions is presented below.

1. Impacts to Tobacco Users

a. Review of CPD Reductions and Anticipated Patterns of Use

As described in Section III(B)(4)(a), individuals who smoke VLNC cigarettes either demonstrate no significant differences in smoking topography relative to those who smoke UB-NNC or NNC cigarettes, or they demonstrate changes in smoking topography measures that are associated with reductions in tobacco smoke exposure (e.g., lower total puff volume).

Additionally, as described in Sections III(B)(4)(b-c), most smokers assigned to use VLNCs in clinical studies dual-used them with UB-NNC cigarettes. Smokers who predominantly use VLNCs—even when dual-using some UB-NNC cigarettes—experience a significant reduction in CPD and reduced dependence scores. The applicant also acknowledges that the likely situation with VLN™ cigarettes would be one where, upon initiation, consumers who want to quit may have difficulty adhering to just smoking VLN™ cigarettes and may initially alternate between UB-NNC cigarettes and VLN™ cigarettes; however, dual use with UB-NNC cigarettes would likely subside over time as smokers acclimate to smoking VLN™ cigarettes.

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). Among smokers motivated to quit, 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, Donny, Hertsgaard, & Hatsukami, 2015; Hatsukami et al., 2010; Walker et al., 2012).

For these reasons, in Section III(B)(4), I conclude that it is reasonably likely that cigarette smokers will experience a reduction in nicotine dependence, which will also reduce tobacco dependence, from using these products.

However, the evidence provided by the applicant suggests that reduced cigarette consumption, rather than complete smoking cessation, is the main benefit of VLN™ cigarettes. However, it is also reasonably likely to infer that reduced nicotine dependence, leading to reduced cigarette consumption, can also lead to increased quit attempts and increased likelihood of future smoking cessation. The applicant

stated that the target market will be current smokers who wish to reduce their nicotine consumption and could potentially reduce cigarette consumption and quit smoking. Since there are no long-term epidemiological studies on cigarette consumption among VLN™ cigarette smokers, the CPD consumption evidence provided by the applicant was based on clinical studies where NNC smokers, with no intention to reduce their nicotine consumption nor quit smoking, were instructed to switch to use VLN™ cigarettes. It is not clear how well CPD findings from clinical studies will generalize to a real-world setting; they could be overestimates or underestimates (as discussed in Section III(B)(c). **FDA used the best evidence available—the longest study of VLNC cigarettes to date—to estimate CPD reductions from using the proposed MRTPs. In this study, total CPD (including study and non-study cigarettes) was reduced by 46-53% in VLNC cigarette smokers compared to NNC cigarette smokers after 20 weeks of use (Hatsukami et al., 2018). Thus, FDA evaluates the potential risk reductions associated with a 50% or more reduction in CPD.** However, it should be noted that smokers who do not reduce their CPD by at least 50% are not expected to reduce risks of negative health effects. Additionally, health risks are found even with consistent low-level smoking (10 or fewer CPD) (Rigotti, 2018).

b. Risk Reductions that are Reasonably Likely Based on Reduced CPD

The medical and epidemiology reviews assessed potential health risk reductions (besides nicotine dependence) from reducing CPD.

While the health benefits of smoking reduction are not as well established as those of smoking cessation, the evidence suggests that 50%+ reductions in CPD may reduce some tobacco-related morbidities other than nicotine dependence, but not others. The relationship between the amount of cigarette smoking and disease is not strictly linear, and smoking reduction does not result in improvement in all health outcomes. For example, Godtfredsen et al. (2003, 2005) examined the effect of smoking reduction on lung cancer risk and found that heavy smokers (≥15 CPD) who reduced CPD by at least 50% had about a 25% reduction in lung cancer risk compared to continuing heavy smokers. While some studies found that a decrease of at least 50% CPD was associated with beneficial effects in some cardiovascular risk factors, such as cholesterol levels, another study found that smoking reduction had no effect on the risk of myocardial infarction (Bollinger, 2000; Bollinger et al., 2002; Eliasson et al., 2001; Hatsukami et al., 2005; Haustein et al., 2004; Godtfredsen et al., 2003). Similarly, while smoking reductions of at least 50% have resulted in improvement in some pulmonary symptoms, studies have not shown robust improvements in lung function or a reduction in the risk of hospitalization for chronic obstructive pulmonary disorder (COPD) (Hatsukami et al., 2005; Stein et al., 2005; Burchfiel et al., 1995; Godtfredsen et al., 2002).

Lee (2013) reviewed 14 studies that examined the effect of smoking reduction on risks of lung cancer, COPD, and CVD. He found that compared to non-reducers, any reduction in cigarette consumption significantly lowered risk of lung cancer but did not significantly reduce risks of CVD, all-cause mortality, smoking-related cancer mortality, and COPD. However, he did not examine this smoking reduction in a specific category reflecting amount of smoking reduction (e.g., any reduction, <50% [reduction], ≥50%); many studies included in this meta-analysis had different smoking reduction categories. Taken together**, published epidemiological studies (e.g., Godtfredsen et al., 2003; Godtfredsen et al., 2005; Lee, 2013; Inoue-Choi et al., 2019; Tverdal & Bjartveit, 2006) assessing the relationship between smoking reduction and disease risks suggest that a reduction in some morbidities is reasonably likely, such as lung cancer risk in those who reduced cigarette consumption by more than 50%, compared to non-**

reducers (Godtfredsen et al., 2005); however, this is not the case for all morbidities (Lee, 2013; Tverdal & Bjartveit, 2006; Godtfredsen, 2008).

Studies have not consistently demonstrated that a reduction in CPD reduces mortality. Godtfredsen et al. (2002) found no change in all-cause mortality, mortality from COPD/respiratory infections, or mortality from CVD in heavy smokers who reduced their tobacco consumption by at least 50% compared to continued heavy smokers in a prospective cohort study. Tverdal & Bjartveit (2006) found similar results with no change in all-cause mortality or mortality due to smoking-related cancer after smoking reduction. However, a recent study evaluating changes in smoking patterns over a longer time period than previous studies found that all-cause mortality was lower among smokers who reduced their CPD compared to those who maintained their CPD, with greater reductions in CPD yielding greater benefits (Inoue-Choi et al., 2019).

These data suggest that compared to continued use of NNC cigarettes, some smokers who switch to VLNCs and reduce their CPD may achieve the health benefits that have been directly associated with a ≥50% reduction in CPD, such as reductions in lung cancer risk. **Thus, in absence of long-term epidemiological studies of the proposed MRTPs, I find that marketing the proposed MRTPs is reasonably likely to reduce some tobacco-related morbidities.**

c. Summary and Conclusion

Below are key findings from the medical and epidemiology reviews regarding potential risk reductions from reducing CPD:

- Smokers who predominantly use VLNCs—even when dual-using some UB-NNC cigarettes—experience a significant reduction in CPD and reduced dependence scores. Previous research has also found that reducing cigarette consumption can increase the likelihood that an individual will become cigarette abstinent in the future.

- Although there is uncertainty in how clinical study data will generalize to the real-world setting, the longest clinical study of VLNCs found that total CPD (including study and non-study cigarettes) was reduced by 46-53% in VLNC cigarette smokers compared to NNC cigarette smokers after 20 weeks of use (Hatsukami et al., 2018). Thus, FDA evaluates the potential risk reductions associated with a 50% or more reduction in CPD.

- Published epidemiological studies assessing the relationship between smoking reduction and disease risks suggests that a reduction in some morbidities is reasonably likely, such as lung cancer risk in those who reduced cigarette consumption by more than 50% compared to non-reducers; however, this is not the case for all morbidities.

- Previous studies have not consistently demonstrated that a reduction in CPD reduces mortality. However, a recent study evaluating changes in smoking patterns over a longer period of time than previous studies found that all-cause mortality was lower among smokers who reduced their CPD compared to those who maintained their CPD, with greater reductions in CPD yielding greater benefits (Inoue-Choi et al., 2019).

As TPL, I agree with these findings. Based on these findings, and in absence of long-term epidemiological studies of the proposed MRTPs, **I find that marketing the proposed MRTPs is**

reasonably likely to reduce some tobacco-related morbidities, in addition to nicotine dependence. Under section 911(g)(2)(A)(iii) of the FD&C Act, to issue an exposure modification order, FDA must find "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 set forth in [section 911(g)(1)]." The available evidence is not sufficient to conclude that the applicant has demonstrated that the products, as 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." There are no long-term epidemiological studies on cigarette consumption among VLN™ cigarette smokers and the CPD consumption evidence provided by the applicant was based on clinical studies where NNC smokers, with no intention to reduce their nicotine consumption nor quit smoking, were instructed to switch to use VLN™ cigarettes. It is not clear how well CPD findings from clinical studies will generalize to a real-world setting; they could be overestimates or underestimates. Thus, there are outstanding questions about the manner in which consumers will use VLN, and if individual tobacco users use VLN cigarettes in the same frequency and manner as conventional cigarettes, they will not significantly reduce harm and their risk of tobacco-related disease. In addition, while the applicant-sponsored studies do not address biomarkers of potential harm (BOPH), one published study on the effect on BOPH of switching from conventional cigarettes to VLNC cigarettes was submitted (Hatsukami et al., 2019). This study did not identify robust changes between the study groups; therefore, no conclusions regarding the short- or long-term health risk of VLN™ cigarettes can be made based on the available BOPH data. In totality, conclusive scientific evidence to meet the standards set forth in section 911(g)(1) is not available.

However, it is reasonably likely that cigarette smokers who use VLN cigarettes will experience a reduction in nicotine dependence, which will also reduce tobacco dependence. Reductions in tobacco dependence can lead to increased tobacco cessation and are anticipated to lead to long-term reductions in exposure to the smoking-related toxicants associated with morbidity and mortality. Using the proposed MRTPs would be reasonably likely to reduce nicotine dependence and a reduction in CPD of at least 50% is associated with a reduction in some tobacco-related diseases (e.g., lung cancer), but not others, supporting a likely overall population health benefit.

Thus, although reduced risk has not been demonstrated, the totality of evidence presented suggests that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies. Therefore, these findings provide additional support for the applications submitted under the 911 (g) (2) reduced exposure standard: 911(g)(2)(A)(iii), which states that where "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 set forth in paragraph (1) ..." [section 911(g)(1)] pursuant to modified risk 911 (g)(1) reduced risk standard.

2. Tobacco Users' Likelihood of Use After Exposure to the Proposed Modified Risk Claims

The applicant's quantitative perception and intention study assessed adult smokers' intentions to try or use the proposed MRTPs after exposure to its proposed modified risk labeling. The findings from these studies are summarized below. More detailed description and analysis can be found in the social science review.

a. Likelihood that Current Smokers will Start Using the Proposed MRTPs

The applicant's research found that many current smokers were interested in VLN™ after viewing pack labeling with the modified risk claims. The applicant's M/A/R/C Quantitative Study (total sample size n=29,219; Protocol #: 5180080-VLN™-B2) randomly assigned participants to view either images of a Marlboro Gold™ cigarette pack or a VLN™ cigarette pack with the proposed modified risk information. Specifically, among participants who viewed the VLN™ pack, they viewed multiple conditions that either contained: Claims #1-3 and the disclaimer; Claims #1, and #3, the disclaimer and "helps you smoke less"; Claims #1, and #3, the disclaimer, and "(b) (4) ." After viewing the cigarette pack, participants reported their intentions to purchase VLN™/ Marlboro Gold™ and their intentions to smoke VLN™/ Marlboro Gold™ "on a regular, ongoing basis." Current smokers reported moderate intentions to purchase both products, with mean intentions to purchase VLN™ well above the midpoint of the scale (mean intentions of approximately 3.4) and mean intentions to purchase Marlboro Gold™ slightly below the midpoint of the scale.

Intentions to purchase VLN™ were substantially higher than intentions to purchase Marlboro Gold™ (by approximately 0.5 on the 5-point scale), a difference that reached statistical significance (M/A/R/C Quantitative Study Report, p. 104). Current smokers also reported substantially higher intentions to use VLN™ on a regular, ongoing basis compared to Marlboro Gold™ (mean intentions of approximately 3.7; M/A/R/C Quantitative Study Report, pp. 103-105).

Intentions to use VLN™ on a regular, ongoing basis were especially high among current smokers intending to quit smoking (mean intentions of approximately 3.8-3.9; M/A/R/C Quantitative Study Report, p. 112). This finding is consistent with the potential for a population health benefit, if current smokers reduce their overall cigarette smoking when using VLN™ cigarettes. Note that the applicant used a broad definition of quit intentions that includes up to two-thirds of current smokers in the U.S. (Persoskie & Nelson, 2013), even though fewer than 10% of smokers might be expected to successfully quit smoking within the next year (Babb, Malarcher, Schauer, Asman, & Jamal, 2017; Messer, Trinidad, Ad-Delaimy, & Pierce, 2008).

Because of an issue in the study design (detailed in Section 5.2 of the social science review), the study's estimates of current smokers' intentions to purchase and use Marlboro Gold™ exclude all of the smokers who already smoke Marlboro Gold™ as their usual brand. Because of this, we do not expect that current smokers would be more likely to purchase and use VLN™ compared to Marlboro Gold™. Rather, a more supportable conclusion is that, among current smokers who try a new brand, trial of VLN™ may exceed trial of Marlboro Gold™.

b. Likelihood that Current Smokers Will Use VLN™ to Cut Down or Quit Smoking

Although the applicant's research on its proposed labeling suggests that marketing VLN™ with the proposed modified risk information would increase use of VLN™ cigarettes among adult current smokers, the applicant provided limited information about *how* current smokers would use VLN™ cigarettes, such as whether they would use VLN™ to substantially reduce their overall smoking frequency.

As noted above in Section 3 ("Evaluating Consumer Understanding"), the proposed LLA do not include statements about using VLN™ to cut down on one's overall cigarette smoking. Rather, the applicant argues that some smokers will choose to replace their current cigarettes with VLN™ and, depending on their efforts to primarily use VLN™, will then reduce their overall smoking frequency (Section 7 "Summary of All Research Findings," p. 29). Indeed, the applicant summarized clinical studies showing that using VLN™ cigarettes leads to "decreased cigarette consumption, reduction in nicotine absorption, reduction in other biomarkers of exposure, more quit attempts, and abstinence" (Executive Summary, p. 2). However, in these studies, smokers who were informed of VLNC cigarettes' very low nicotine content were also given instructions for how to use VLNC cigarettes (e.g., they were told to smoke VLNC cigarettes and not smoke their usual brand cigarettes [6-Week Clinical Switching Study CA24914], or they were provided with VLNC cigarettes as part of a smoking cessation program [McRobbie et al., 2016]). To our knowledge, none of those studies provided participants with information comparable to the proposed modified risk LLA, which inform people about the reduced nicotine content without instructing participants to use VLN™ cigarettes to cut down on their smoking (or to try to primarily use VLN™ cigarettes rather than their other cigarettes, which facilitates smoking fewer cigarettes overall). Without providing information about the conditions of use for VLN™ cigarettes (e.g., "Helps you smoke less"), it is unclear whether smokers will understand the intended conditions of use and the need to cut down in order to obtain benefits from the reduced nicotine content in VLN™ cigarettes.

Beyond the clinical studies discussed above, the applicant's consumer perception research provides limited additional information about smokers' intentions to use VLN™ as a substitute for other cigarettes or to cut back on smoking. Specifically, the M/A/R/C Quantitative Study asked the following question among current smokers who reported that they might purchase VLN™ and Marlboro Gold™: "Would your purchase(s) of [VLN™/ Marlboro Gold™] replace any tobacco or nicotine-replacement products that you currently use?" The majority of smokers who reported that they might purchase VLN™ responded, "Yes, buying VLN™ would result in fewer purchases of other tobacco or nicotine-replacement products." Specifically, among current smokers intending to quit, over 80% expected that buying VLN™ would result in fewer purchases of other tobacco or nicotine-replacement products, compared to only 58% for Marlboro Gold™; among current smokers not intending to quit, 64% expected that buying VLN™ would result in fewer purchases of other tobacco or nicotine-replacement products, compared to only 42% for Marlboro Gold™. Smokers intending to quit were more likely than smokers not intending to quit to report that their VLN™ purchase would result in fewer purchases of other tobacco or nicotine-containing products (which was also observed for intended purchases of Marlboro Gold™), which is consistent with the expectation that intended quitters would be unlikely to want to increase their overall cigarette consumption.

When smokers were asked which products they would cut back on as a result of buying VLN™, almost all chose cigarettes (approximately 90%), and few chose NRT (1-4% across smokers intending and not

intending to quit; M/A/R/C Quantitative Study Report, p. 115). These findings suggest that, if VLN™ is marketed with the proposed modified risk information, many smokers would be interested in purchasing VLN™ to replace at least some of their cigarette purchases. However, the applicant's consumer research provides no information about whether smokers intend to use VLN™ cigarettes to cut down on their overall cigarette consumption or simply replace all or some of their current cigarette use with VLN™ cigarettes. **Including the phrase "Helps you smoke less" as discussed in Section III(C)(2) of this review would address this issue. Findings also suggest that, after viewing the proposed modified risk labeling, few smokers planned to use VLN™ instead of NRT, including smokers intending to quit.**

c. Likelihood that Current Smokers Will Use VLN™ Instead of Quitting Smoking

The majority of studies on VLNC cigarettes were conducted in participants not interested in quitting, which does not accurately reflect the population of smokers most likely to use VLN™ cigarettes (i.e., those interested in reducing cigarette consumption). However, some studies from the literature discussed in Appendix 2 of the BCP review find that among smokers motivated to quit, VLNC cigarettes may facilitate abstinence due to reduced nicotine exposure. Using NRT and behavioral intervention with VLNC cigarettes may aid in cessation in some smokers motivated to quit. In smokers not motivated to quit, smoking VLNC cigarettes did not increase motivation to quit compared to UB-NNC cigarette smokers, although quit attempts were greater among those assigned to smoke VLNC cigarettes. However, VLN™ cigarettes may appeal to smokers interested in quitting. This consumer subset may be motivated to use VLN™ cigarettes to reduce nicotine consumption, and as a result, VLN™ cigarettes may potentially aid in facilitating cessation. It is unlikely that current tobacco users who are not interested in quitting will completely switch to VLN™ cigarettes or a smoking cessation product, such as NRT. However, smokers motivated to reduce their cigarette consumption may be more likely to switch completely to VLN™ cigarettes or attempt to quit smoking with concurrent use of NRT and behavioral intervention.

In addition, given that quitting behaviors may also depend, in part, on whether smokers understand VLN™ cigarettes' health risks and conditions of use, if FDA authorizes the applicant to market VLN™ cigarettes with the proposed claims, **I recommend that the order require that all modified risk LLA display the intended conditions of use for VLN™ cigarettes, "Helps you smoke less," to clarify the purpose of VLN™ cigarettes.** If smokers misunderstand the proposed modified risk information to mean that VLN™ cigarettes are less toxic than other cigarettes and present lower risks even when smoked in the same way, previously published research suggests the theoretical possibility that this could reduce smokers' intentions to quit. For example, in a nationally representative study of U.S. adult smokers, those who believed that VLNC cigarettes were less carcinogenic than other cigarettes were more likely than other smokers to say that a very low nicotine standard (i.e., a standard limiting the nicotine content in all cigarettes) would reduce their likelihood of quitting smoking (Byron et al., 2018). Also, prior research on cigarettes and other tobacco products has found that perceptions of product risk predict whether current users will continue using the products (e.g., Brose et al., 2015; Elton-Marshall et al., 2020). Thus, although data on VLN™'s abuse liability and clinical effects suggest that VLN™ would not deter quitting, we expect that providing the intended conditions of use will enable smokers to understand VLN™'s health risks and purpose and avoid negatively influencing smokers' intentions to quit.

d. Vulnerable population: Impact of marketing on people with mental health issues

The epidemiology review did not identify analyses by the applicant that specifically focus on vulnerable populations that are at increased risk of using VLN™ cigarettes. The applicant provided an evaluation of the use of VLNC on smoking behaviors of a vulnerable population (individuals with depression, schizophrenia, and psychiatric disorders). These studies showed that as a result of switching from traditional cigarettes to VLNC cigarettes, participants reduced CPD without compensatory smoking.

The BCP review states that the evidence on vulnerable populations is extrapolated from the larger VLNC cigarette literature. The effects of VLNC cigarettes have been assessed in two vulnerable populations: smokers with mental health symptoms (e.g., depression, schizophrenia) and adolescent smokers. Effects on adolescent smokers are further discussed in the subsequent section on ' *Tobacco Nonusers' Likelihood of Use After Exposure to the Proposed Modified Risk Claims: Impact of Marketing on Youth'*. The literature supports that in smokers with mental health symptoms, as in the general population, VLNC cigarettes were associated with smaller reductions in craving and withdrawal symptoms compared to NNC cigarettes. Among this group, VLNC cigarettes were not associated with increased markers of compensatory smoking (e.g., smoking topography, CO) compared to the general population. 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. Studies also found no evidence that alcohol or marijuana use moderates the effects of VLNC cigarettes, and VLNC cigarette use does not increase compensatory alcohol or marijuana use. In sum, the available literature provides little to no evidence that VLN™ King cigarettes increase risk of adverse effects (e.g., exacerbations of psychiatric symptomatology, other substance use) in smokers with mental health symptoms. Extrapolating from the literature on NNC menthol cigarettes, evidence does not suggest that menthol would differentially influence outcomes in vulnerable populations evaluated for VLNC non-menthol cigarettes. As such, the literature can also be extrapolated to VLN™ Menthol King cigarettes and indicates little to no evidence that VLN™ Menthol King cigarettes would increase risk of adverse effects in vulnerable populations. There is no evidence of increased aversive effects (e.g., enhanced withdrawal, exacerbation of psychiatric symptoms) from smoking VLNC cigarettes (menthol or non-menthol) among vulnerable smoking populations (e.g., those with mental illness) compared to smoking NNC cigarettes.

e. Summary and Conclusion

Below I describe social science's key findings related to tobacco users' likelihood of use after exposure to the proposed modified risk information:

- Current smokers reported moderate intentions to purchase both VLN™ cigarettes and Marlboro Gold™, with mean intentions to purchase VLN™ cigarettes well above the midpoint of the scale. Among current smokers who try a new brand, trial of VLN™ cigarettes may exceed trial of Marlboro Gold™. Intentions to purchase and intentions to use on a regular, ongoing basis were substantially higher for VLN™ cigarettes than for Marlboro Gold™. Intentions to use VLN™ cigarettes on a regular, ongoing basis were especially high among current smokers intending to quit smoking.

- To evaluate the likelihood that current smokers will use the product to cut back or quit smoking, social science first evaluated the product labeling, and noted that it did not include information instructing users to cut down on their smoking or to try to primarily use VLN™ cigarettes. Without providing information about the conditions of use for VLN™ cigarettes (e.g., "Helps you smoke less"), it is unclear whether smokers will understand the intended conditions of use and the need to cut down or reduce cigarette smoking in order to obtain benefits from the reduced nicotine content in VLN™ cigarettes.

- There is some evidence that smokers intending to quit expected that buying VLN™ cigarettes would result in them cutting back on buying other cigarettes. Among current smokers intending to quit who expressed they might purchase VLN™, over 80% expected that buying VLN™ would result in fewer purchases of other tobacco or nicotine-replacement products, compared to only 58% for Marlboro Gold™; among current smokers not intending to quit, 64% expected that buying VLN™ would result in fewer purchases of other tobacco or nicotine-replacement products, compared to only 42% for Marlboro Gold™. When smokers were asked which products they would cut back on as a result of buying VLN™ cigarettes, almost all chose cigarettes (approximately 90%), and few chose NRTs.

- Most clinical studies of VLNCs are conducted among smokers who do not intend to quit. However, some studies indicate that among smokers motivated to quit, VLNC cigarettes may facilitate abstinence due to reduced nicotine exposure. Using NRT and behavioral intervention with VLNC cigarettes may aid cessation in some smokers motivated to quit.

- The literature supports that in smokers with mental health symptoms, as in the general population, VLNC cigarettes were associated with smaller reductions in craving and withdrawal symptoms compared to NNC cigarettes. Among this group, VLNC cigarettes were not associated with increased markers of compensatory smoking (e.g., smoking topography, CO) compared to the general population.

As TPL, I agree with these findings. Based on this information, I find it likely that smokers will have interest in trying the proposed MRTPs when they are marketed with the proposed claims. Furthermore, I find it possible that consumers will not understand how to use the product to get the likely risk reduction; therefore, **I recommend that the order require that all modified risk LLA display the intended conditions of use for VLN™ cigarettes, "Helps you smoke less," to clarify the purpose of VLN™ cigarettes.** Additionally, I find that smokers motivated to quit are not likely to engage in sustained use of this product instead of quitting, as smokers intending to quit who are interested in this product plan on cutting down purchases of NNC cigarettes, and as VLNC cigarettes may facilitate abstinence. **Together, these findings are supportive that marketing VLN™ cigarettes with these reduced exposure claims could appeal to current smokers who are most likely to benefit from their use, and this supports a likely benefit to population health.**

3. Tobacco Nonusers' Likelihood of Use After Exposure to the Proposed Modified Risk Claims

The impact on tobacco use behavior among current users must be considered alongside the potential effects on tobacco use initiation among non-users. The applicant assessed the potential impact of marketing VLN™ cigarettes with the proposed modified risk claims among current non-users by including adult former smokers and never smokers in its consumer perception studies. The applicant did not provide any direct data on the potential for use or appeal among U.S. youth. A summary of the relevant findings is presented below and provided in more depth in the social science and BCP reviews.

a. Adult Never and Former Smokers, including Young Adults and Recent Quitters

The applicant's research suggests that marketing VLN™ cigarettes with the proposed modified risk information on the product labeling has the potential to slightly increase the use of VLN™ cigarettes among never and former smokers, but that rates of use would be low. Specifically, the M/A/R/C Quantitative Study (total sample size n=29,219; Protocol #: 5180080-VLN™-B2) randomly assigned participants to view either images of a Marlboro Gold™ cigarette pack or a VLN™ cigarette pack with the proposed modified risk information. Specifically, among participants who viewed the VLN™ pack, they viewed multiple conditions that either contained: Claims: #1-3 and the disclaimer; Claims #1, and #3, the disclaimer and "helps you smoke less;"; Claims # 1, and #3, the disclaimer, and (b) (4) (b) (4) After viewing the cigarette pack, participants reported their intentions to "smoke [VLN™/ Marlboro Gold™] on a regular, ongoing basis," and their intentions to purchase VLN™/ Marlboro Gold™. Former and never smokers' mean intentions to purchase both products were near the bottom of the scale (for VLN™, approximately 1.3-1.4 on the 6-point scale). Intentions to purchase VLN™ were slightly higher than intentions to purchase Marlboro Gold™, a difference that reached statistical significance given the study's large sample size (M/A/R/C Quantitative Study Report, p. 104). Never smokers (but not former smokers) also reported significantly higher intentions to smoke VLN™ on a regular, ongoing basis compared to Marlboro Gold™, with mean intentions again near the bottom of the scale (for VLN™, approximately 1.3-1.4 on the 5-point scale; M/A/R/C Quantitative Study Report, p. 103).

Results among subgroups at increased risk of tobacco use were similar to those above, with slightly higher intentions among never smokers who are *young adults* (aged 18-25 years-old; compared to older adult never smokers; i.e., mean intentions to purchase VLN™ and use VLN™ of approximately 1.5; M/A/R/C Quantitative Study Report, p. 108) and considerably higher intentions among former smokers who *quit recently* (compared to long-term quitters; i.e., mean intentions to use VLN™ cigarettes of approximately 2.0; M/A/R/C Quantitative Study Report, p. 109).

The above findings suggest the potential for a low, but still notable, level of trial of VLN™ cigarettes among adult former and never smokers if marketed with the proposed modified risk information. As the applicant states, Marlboro Gold™ was selected as a comparator product because it is currently on the market and has known use rates (M/A/R/C Quantitative Study Protocol, p. 18). Specifically, based on 2017 sales data, Marlboro is the leading cigarette brand in the U.S., with sales volume accounting for approximately 40% of total cigarette sales and consumption (CDC, 2019; Sharma et al., 2016). Also, the item assessing intentions to use VLN™ included the following potentially biasing text: "By intent to use, we mean that you personally, as a non-smoker, now intend to smoke VLN™ on a regular, ongoing basis"

(emphasis added). This text may have implied to former and never smokers that they should *not* intend to smoke VLN™ cigarettes on a regular, ongoing basis because they are non-smokers.

b. Impact of Marketing on Youth

The application did not provide information about the likelihood that youth would use VLN™ cigarettes if marketed with the proposed modified risk information. After considering the factors outlined below and considering the youth marketing restrictions outlined in the PMTA order letters, FDA has low concern about youth initiation and progression to regular use.

The BCP review notes that existing data in adolescent and young adult smokers suggest VLNC cigarettes are associated with lower positive subjective effects ratings (e.g., liking, pleasant, satisfaction) compared to NNC cigarettes, and VLNC cigarettes are not associated with compensatory smoking (i.e., smoking topography, TNE levels) in this vulnerable population. It is important to note that most of the data come from acute laboratory studies where participants have limited VLNC cigarette exposure. However, a secondary analysis of the Donny et al. study found no evidence of differential effects of VLNC cigarettes as a function of age (i.e., 18-24 years vs. 25+ years). While nicotine dependence has been shown to develop rapidly among adolescents following exposure to NNC cigarettes, the limited available evidence on VLNC cigarettes suggests that youth who experiment with VLNC cigarettes may find them less appealing and may be less likely to develop nicotine dependence and become established cigarette smokers due to their lower abuse liability profile.

Additionally, Cassidy and colleagues (2019) conducted a secondary analysis of Cassidy et al. (2018) to evaluate the abuse liability of VLNC cigarettes using a behavioral economic measure. Participants were 50 adolescent smokers who completed five hypothetical Cigarette Purchase Tasks (usual brand, and 15.8, 5.2, 1.3, 0.4 mg nicotine/g tobacco SPECTRUM cigarettes) after sampling a single cigarette of each dose. For each purchase task, participants were asked to estimate how many cigarettes they would smoke in a given day at escalating prices if the given cigarette was the only tobacco product available. Each of the SPECTRUM research cigarettes were associated with lower demand (i.e., abuse liability) compared to usual brand cigarettes; however, there were no differences in demand as a function of SPECTRUM cigarette dose. The Cassidy et al. (2019) study shows that among this group of adolescents, the reinforcing efficacy or appeal of all doses of SPECTRUM cigarettes was lower compared to UB-NNC cigarettes. This result contrasts with primary outcomes showing reduced subjective effects as a function of reduced nicotine content in SPECTRUM cigarettes. The lack of a dose-response effect in this study may be due to adolescents' sensitivity to cigarette branding, or their inability to discriminate between the research cigarettes after a single, blinded exposure. It is also possible that the Cigarette Purchase Task used in this study was less sensitive to dose-dependent differences in appeal, compared to measures that directly assess subjective response. In all, this 2019 study supports the available evidence showing that VLNC cigarettes are not associated with increased appeal compared to UB-NNC or NNC cigarettes among adolescent smokers. In all, each of the SPECTRUM research cigarettes was associated with reduced abuse liability compared to usual brand cigarettes in this group of adolescent smokers.

Several additional factors suggest that, depending on how VLN™ cigarettes are marketed, effects on youth may be limited. Most notably, youth cigarette smoking rates declined between 2002 and 2010 (Johnston et al., 2019), a period when Quest cigarettes were on the U.S. market and advertised as "low nicotine," "extra low nicotine," and "nicotine free," and as products that allowed people to "enjoy smoking without all of the Nicotine" (Shadel et al., 2006; Strasser et al., 2008). In addition, a study in a

convenience sample of college students found that, after viewing ads for Quest, Eclipse (a heated cigarette), and Marlboro, the students rated Quest cigarettes as lower than Marlboro Lights and Eclipse on a scale of positive expectancies (including, for example, satisfying, fun, exciting, interesting) that predicted willingness to try each type of cigarette (O'Connor et al., 2007). However, generalizability from such studies is limited because of potential differences in the proposed LLA for VLN™ cigarettes. For example, the applicant proposed to use different modified risk claims than those used for Quest, as well as ads that may differ in their appeal, targeting, and dissemination. Recent changes in the advertising landscape – in particular the rise of social media as a platform for reaching young audiences – also raise the possibility that VLN™'s modified risk advertising could have different effects on youth compared to Quest's advertising from the 2000s. Therefore, it is possible that the marketing of these products could increase youth appeal and the likelihood that youth may believe that these cigarettes might be "safer" than NNC cigarettes, initiate use with them, and even transition to NNC cigarette smoking. Accordingly, the marketing for VLN™ cigarettes should avoid the use of youth appealing ads or imagery and should be targeted to reach adult smokers. We also note that the PMTA order for these identical products, issued in December 2019, includes restrictions on marketing to limit youth exposure.

c. Summary and Conclusion

Below I describe social science's key findings related to tobacco nonusers' likelihood of use after exposure to the proposed modified risk information:

- The applicant's research suggests that marketing VLN™ with the proposed modified risk information on the product labeling has the potential to slightly increase the use of VLN™ cigarettes among never and former smokers, but that rates of use would be low. Intentions to purchase and smoke VLN™ cigarettes on a regular, ongoing basis were low, though slightly higher than for Marlboro Gold™. Intentions among young adults aged 18-25 were slightly higher, but still low. Recent quitters had slightly higher intentions to use VLN™ cigarettes, though they were still below the midpoint of the scale.

- The application did not provide information about the likelihood that youth would use VLN™ cigarettes if marketed with the proposed modified risk information. However, at this time, based on the available evidence, the risk of youth initiation and progression to regular use appears to be low because: the products have low abuse liability and youth may be less likely to develop nicotine dependence using them; young adults rate VLNCs as having lower subjective effects ratings compared to NNC cigarettes; and a study of adolescents found that the reinforcing efficacy or appeal of all doses of VLNC cigarettes was lower compared to UB-NNC cigarettes.

As TPL, I agree with these findings. Based on this information, **I find it likely that nonsmokers will have low interest in trying the proposed MRTPs when they are marketed with the proposed claims**. This provides support for the required findings in section 911(g)(2)(A)(i) that "[the] order would be appropriate to promote the public health" and section 911(g)(2)(B)(iv) that "[the] order is expected to benefit the health of the population as a whole") Concerns related to youth initiation and progression to regular use of these proposed MRTPs are low; however, given that youth are at increased risk, generally, for initiating tobacco use and the potential effect of modified risk information on youth use, it is critical that a marketing plan for the products be designed to target tobacco users and prioritize preventing youth exposure. Studies suggest that perceptions of risk predict tobacco product use among youth (Song

et al., 2009) (Strong et al., 2019). It is important to note that FDA's marketing authorization order for the same products (but without modified risk information) (PM0000491-PM0000492) includes requirements intended to help ensure that the marketing of the products will continue to be appropriate for the protection of the public health, taking into account initiation among non-users, particularly youth. This includes providing FDA with advertising and marketing plans, including plans to restrict youth access and limit youth exposure to the products' labeling, advertising, marketing, and/or promotion. In addition, the applicant is required track and measure actual delivery of all advertising impressions, including among youth.

4. Population Health Impact Model

The applicant provided a population model estimating the public health impacts of VLN™ cigarettes. Epidemiology assessed the data inputs and assumptions concerning tobacco use behaviors including smoking prevalence, all-cause mortality, and life-years saved with and without use of VLN™ cigarettes.

In Section VIII.F "Effect on the Population as a Whole," the applicant presented two objectives, which were: (1) to predict conventional cigarette (CC) and VLN™ cigarette smoking according to the current regulatory framework; and (2) to show the effect of potentially increased smoking cessation and CPD reduction by VLN™ smokers, with the final endpoints being smoking prevalence and cigarette-attributable deaths (life-years gained) with VLN™ cigarettes on the market through year 2100. The simulation model assessed the possible effects of the proposed VLN™ cigarettes on US population health. This model projects smoking prevalence (Figure VIII.F-5), avoided cigarette-attributable deaths (Figure VIII.F-6), and life-years gained (Figure VIII.F-6) with VLN™ products potentially on the market. The applicant also provided more details about the model inputs and results in the Summary Report, "A Simulation Model to Evaluate the Impact of VLN™ Cigarettes on the Population as a Whole." The figures and table numbers in this part of the review reflect those used in applicant's Summary Report.

The applicant used a Markov state dynamic population model to estimate the impact of introducing VLN™ cigarettes on the U.S. market. In terms of smoking inputs, the applicant used data from the National Health Interview Survey (NHIS) and National Survey on Drug Use and Health (NSDUH), which represent the U.S. population, to derive smoking initiation rates for CC smokers. For the VLN™ smoking initiation rate, the applicant assumes that the market share of CC and VLN™ will be equalized at approximately 25% by the year 2050, meaning that 7.1% of CC smokers will initiate VLN™ smoking per year (i.e., if 7.1% of CC smokers switch to VLN™ cigarettes every year until 2050, 25% of smokers will be using VLN™ cigarettes by 2050).

Key model inputs include:

- Population: The applicant used 2015 U.S. Census estimates to project the population for years 2016 to 2060 by age and sex.

- Smoking behavior: The applicant calculated conventional cigarette (CC) smoking initiation rates based on prevalence of established smoking from age 18-24 from the 2015 NHIS data. The applicant estimated quit rates for VLN™ cigarettes using the continued abstinence rates from

Walker et al. (2012), which showed that 33% of VLNC smokers and 28% of non-VLNC smokers remained abstinent six months after quitting.

- Initiation: With regard to VLN™ cigarette smoking initiation, the applicant stated that former and never smokers would not be attracted to VLN™ cigarettes based on the consumer perception study. The applicant estimated the initial VLN™ cigarette uptake rate from CC rates based on the 25% market share by 2050: 50% of initial VLN™ cigarette smokers will sustain use after one year, and 10% of initial VLN™ cigarette smokers will relapse back to CC smoking per year.

- CPD changes: The applicant estimated that 80% of VLN™ cigarette smokers will reduce CPD by 50%. The applicant referenced Figure 2 of the Hatsukami et al. (2018) study, which depicted the proportion of smokers who will reduce CPD by at least 50%. All VLN™ smokers will experience the same excessive relative risk (ERR) as CC smokers.

- Mortality: The applicant estimated the all-cause mortality rates by age group, sex, and smoking status. Mortality rates for current smokers were based on CPD. The applicant used data from Poland et al. (2017), Thun et al. (2013), and Bjartveit et al. (2005), to estimate models on CPD consumption and mortality.

Key model assumptions include:

- The applicant stated that use of CC or VLN™ cigarettes will be interpreted as predominant use rather than exclusive use. Instead, the applicant modeled the transition rates of CC smoking to "initial VLN™ smoking" and "initial VLN™ cigarette smoking" to "sustained VLN™ cigarette smoking." In the model, dual use of VLN™ cigarette and CC smoking was not considered explicitly.

- Non-combusted tobacco use (e.g., smokeless tobacco, ENDS) was not modeled. The applicant stated that declining rates of CC smoking over time could reflect dual use with non-combusted products.

- VLN™ cigarette smokers could have different quit rates, CPD, and relative risks compared to CC smokers.

- CC smokers have a fixed number of CPD over time; however, CPD reduction among VLN™ cigarette smokers vary.

- Market share of VLN™ cigarettes will reach 25% by 2050 (i.e., if 7.1% of CC smokers switch to VLN™ cigarettes every year until 2050, 25% of smokers will be using VLN™ cigarettes by 2050).

The applicant provided estimates of six scenarios with different CC quit rates of VLN™ cigarette smokers relative to CC smokers and long-term relapse rates of VLN™ cigarette smoking back to CC smoking:

- Scenario 1 (Base): 118% quit rate and 10% relapse rate

- Scenario 2 (Low-Low, Pessimistic): 100% quit rate and 20% relapse rate

- Scenario 3 (Low-Base, Intermediate 1): 100% quit rate and 10% relapse rate
- Scenario 4 (High-Base, Intermediate 2): 150% quit rate and 10% relapse rate
- Scenario 5 (High-High, Optimistic): 150% quit rate and 0% relapse rate
- Scenario 6 (Mandate in 2020): 100% quit rate and 0% relapse rate

The applicant proposed a population model that assumes that market penetration of VLN™ cigarettes will reach 25% by 2050 and predicts cumulative 340,000 avoided cigarette-attributable deaths by 2100 in the base scenario with introduction of VLN™ cigarettes. However, when Quest 3 cigarettes (VLNC cigarettes) were on the U.S. market in the early 2000s, a lower uptake of this product (nearly zero) was observed compared to other cigarettes (O'Connor et al., 2007). Thus, the 25% market share of VLN™ cigarettes is likely to be an overestimation. Additionally, the applicant stated that the target market is current CC smokers who wish to reduce their nicotine consumption; possible outcomes of switching to VLN™ cigarettes include reducing cigarette consumption and increasing cessation. However, some model assumptions are based on clinical studies that required participants to smoke VLN™ cigarettes (instructed to switch to VLN™ cigarettes), with no intention to quit smoking, and provided compensation to do so; these estimates may be different from observational studies.

Additionally, the model did not address the dual use of CC and VLN™ cigarettes explicitly. Nardone et al. (2016), showed that higher non-compliance was observed with VLNC cigarette smokers, which suggests that a higher proportion of dual use of CC and VLN™ cigarettes could occur. Additionally, if uptake of VLN™ cigarettes by consumers is lower and CC smokers do not switch completely to VLN™ cigarettes right away, the outcomes noted above might take more time; dual use of CC and VLN™ cigarettes would be expected until complete switching occurs. On the other hand, assuming that dual use of CC and VLN™ cigarettes would not happen means that CC smokers would have to quit CC smoking completely before switching to VLN™ cigarettes. The applicant did not incorporate this information in the model assumption.

The applicant provided projections of avoided cigarette-attributable deaths and life-years gained (Table 3 of the Summary Report) with six different scenarios. However, the applicant did not provide the 95% confidence intervals of these projections. It is possible that these projections could overlap with each other. Instead, the applicant provided sensitivity analysis results of different magnitudes of smoking reduction. Moreover, the applicant provided the relative risks of CPD consumption and mortality rate. Previous studies have shown that smoking reduction is not proportional to risk reduction (Godtfredsen et al., 2005; US Centers for Disease Control and Prevention, 2010). Additionally, dual users of CC and VLN™ cigarettes may present different risks compared with exclusive VLN™ cigarette smokers. Thus, the applicant provided an overestimate of magnitudes of smoking reduction among VLN™ cigarette smokers.

Additionally, it is unclear whether the population model forecasts the impact of the availability of proposed MRTP claims. Therefore, it is unclear whether the projected estimates are interpreted as resulting from introduction of the products into the marketplace through the PMTA marketing order or would also require authorization of the MRTPs.

a. Summary and Conclusion

Below are key findings regarding the applicant's population model from the epidemiology review:

- According to the projected population health impact of VLN™ cigarettes presented by the applicant, the health impact of VLN™ cigarettes would result in 340,000 avoided cigarette-attributable deaths by year 2100, if the applicant's projected market share of the product is attained. While clinical studies suggest that CC smokers could reduce cigarette consumption by switching to VLN™ cigarettes, as described in Section III(D)(1) of this review, it is unclear how these estimates will generalize to a real-world setting.

- FDA is not aware of any observational studies examining the use of VLN™ cigarettes among adults and youth. The applicant did not account for youth and vulnerable populations in its model. However, the uptake of VLN™ cigarettes among nonusers (including youth) is likely to be low because of the low abuse liability.

- Based on this model, there are likely to be some benefits of CC smokers switching to VLN™ cigarettes and low uptake of nonusers. However, the model's projected benefits may be overestimated (e.g., high projected market share, dual users of CC and VLN™ cigarettes); model assumptions about tobacco use behavior and risks do not reflect what would likely happen in a real-world population.

As TPL, I agree with these findings. While the applicant's model likely overestimates population health benefit, **I still expect the marketing of the proposed MRTPs to benefit the population as a whole**, as nonsmokers are unlikely to initiate and progress to regular use with VLN™ cigarettes, and even smokers who dual use VLN™ cigarettes with NNC cigarettes are likely to reduce their CPD. Additionally, it is unclear whether the model considered the impact of marketing the product with modified risk claims; accounting for this may increase the estimated uptake of the proposed MRTPs by current smokers.

IV. Conclusions and Recommendations

A. Review Conclusions – Exposure Modification Order Request

The applicant has requested an exposure modification order under section 911(g)(2) of the FD&C Act to market these products as follows:

- Claim #1: "95% less nicotine."

- Claim #2: "Helps reduce your nicotine consumption."

- Claim #3: "...greatly reduces your nicotine consumption."

Additionally, FDA identified the following claims in the advertising the applicant submitted:

- Claim #4: "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 0.27 mg of nicotine."

- Claim #5: “Without exception, VLN™ cigarettes contain at least 95% less nicotine than the top 100 cigarette brands in the United States.”

- Claim #6: “22nd Century’s VLN™ cigarettes contain an average of 0.27 mg nicotine - -at least 95% less nicotine compared to conventional cigarettes.”

- Claim #7: “22nd Century’s VLN™ cigarettes feature the same nicotine content as the lowest nicotine style of the Company’s SPECTRUM research cigarettes.”

- Claim #8: “VLN™ cigarettes contain 0.27 ± 0.1 mg nicotine.”

- Claim #9: “As a result of our unique technology and plant breeding expertise, VLN™ tobacco grows with 95% less nicotine than conventional tobacco.”

- Claim #10: Several examples utilize a graph depicting nicotine levels of VLN™ cigarettes compared to several other cigarette brands.

FDA may issue an exposure modification order under section 911(g)(2) of the FD&C Act (the "special rule") if it determines that the applicant has demonstrated that:

- 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;

- 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 obtaining an order under section 911(g)(1); and

- The scientific evidence that is available without conducting long-term epidemiological studies demonstrates that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies (section 911(g)(2)(A) of the FD&C Act).

Furthermore, for FDA to issue an exposure modification order, FDA must find that the applicant has demonstrated that:

- The magnitude of overall reductions in exposure to the substance or substances that 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 or substances;

- The product as actually used by consumers will not expose them to higher levels of other harmful substances compared to the similar types of tobacco products then on the market unless such increases are minimal and the reasonably likely overall impact of use of the

product 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 (section 911(g)(2)(B) of the FD&C Act).

In making the determinations under section 911(g)(2) of the FD&C Act, FDA must take into account:

- The relative health risks to individuals of the modified risk tobacco product;

- The increased or decreased likelihood that existing tobacco product users who would otherwise stop using such products will switch to using the modified risk tobacco product;

- The increased or decreased likelihood that persons who do not use tobacco products will start using the modified risk tobacco product;

- The risks and benefits to persons from the use of the modified risk tobacco product 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 (section 911(g)(4) of the FD&C Act).

In short, unlike the section 911(g)(1) standard, which requires scientific evidence showing actual risk reduction (e.g., a finding that the product, as actually used by consumers, *will significantly reduce* harm and risk to individual users; a finding that the product, as actually used by consumers, *will benefit* the health of the population a as whole); section 911(g)(2) establishes a lower standard, which allows FDA to issue an order when risk reduction has not yet been demonstrated but is reasonably likely based on demonstrated reductions in exposure (e.g., a finding that a reduction in morbidity or mortality among individual users is *reasonably likely* in subsequent studies; a finding that issuance of an order is *expected* to benefit the health of the population as a whole).

Furthermore, FDA must ensure that the advertising and labeling of the MRTP enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation to all of the tobacco-related diseases and health conditions (section 911(h)(1) of the FD&C Act).

To the extent possible, the assessment integrates the various threads of evidence regarding the product and its potential effects on health and tobacco use behavior, including tobacco use initiation, to determine both the net effect of the product on overall tobacco-related morbidity and mortality and the distribution of the benefits and harms across the population. This determination also considers these

product applications in the context of the current marketplace where menthol cigarette products are legally sold to consumers. In particular, the recommendation considers that VLN™ Menthol King provides an opportunity for menthol smokers to reduce their nicotine consumption and reduce their exposure to nicotine, potentially decreasing their cigarettes per day smoked.

After conducting a thorough scientific review of the information contained in the MRTPAs; the recommendations from the Tobacco Products Scientific Advisory Committee; comments, data, and information submitted to FDA by interested persons; and other scientific information identified by the agency from other sources, I conclude that:

- With respect the exposure modification order request, the applicant **has demonstrated** that the products sold or distributed with the proposed modified risk information meet the standard under section 911(g)(2) of the FD&C Act, including that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies, and issuance of an 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.

Reduced exposure claim substantiation

After conducting a thorough assessment of the scientific evidence, I find that the proposed modified risk claims are substantiated. This includes the applicant-submitted Claims #1-3 and the FDA-identified Claims #4-10. Here, I summarize the evidence supporting the substantiation of each claim, grouped by topic. First, I discuss claims related to nicotine content (Claims #1, 4, 5, 6, 7, 8, 9, and 10), and then I discuss claims related to reduction in nicotine consumption (Claims #2 and 3).

Several lines of evidence substantiate the claims related to nicotine content (Claims #1 and 4-10). First, the chemistry review found that the applicant provided a survey of 100 top-selling cigarette brands that represent 87% of all cigarettes sold in the U.S. through convenience stores in 2017. These 100 cigarette brands contain a reported average of 19.4 mg nicotine per gram of tobacco on a dry weight basis (DWB), and a reported average of 12.0 mg nicotine per cigarette. The applicant reported that the tobacco nicotine content of all 10 batches of the two new VLN™ cigarettes met the applicant's maximum nicotine specification of (b) (4) mg/g on a DWB. Accordingly, the reported nicotine contents of the VLN™ cigarettes are 98% lower than the average reported nicotine contents of the top 100 cigarette brands determined both per gram of tobacco and per cigarette. In addition, both applicant-contracted and FDA nicotine test results found that nicotine levels in tobacco and mainstream smoke of VLN™ cigarettes are at least 96% lower than the majority of marketed and market-leading conventional cigarette brands.

Furthermore, while batch analysis of eight batches of VLN™ cigarettes shows a slightly higher nicotine content than the 0.27 mg/cig reported by the applicant (it was 0.29 mg/cig), this is within the advertised nicotine content lower and upper limit of 0.27 ± 0.10 mg/cig (0.17 and 0.37 mg/cig lower and upper limit). Based on this evidence, Claims #1, 4, 5, 6, 8, and 10 are supported. Finally, the chemistry review notes that the two VLN™ cigarette products contain only Vector 21-41 Burley tobacco, which is a unique tobacco variety not present in any commercially-marketed cigarette tobacco. This tobacco type is genetically engineered using the applicant's proprietary technology to block several genes, which results in suppression of nicotine biosynthesis. This tobacco is also the filler in SPECTRUM research cigarettes NRC102 and mentholated NRC103. SPECTRUM NRC102 and NRC 103 also have less than 0.7 mg/g of

nicotine on a DWB, and thus has at least 95% less nicotine than the reported nicotine content for conventional cigarette tobacco. Thus, Claims #7 and 9 are supported.

Claims #1, 5, 6, and 9 all include the phrase "95% less nicotine." All but one of these claims—Claim #1—indicates the product *contains* 95% less nicotine. Claim 1 does not use the word "contains" and could therefore be referring to nicotine exposure after using the product. Accordingly, the behavioral and clinical pharmacology (BCP) review evaluated the substantiation of this meaning. The applicant's abuse liability studies, which contained actual use data in healthy adult smokers after *ad libitum* and controlled VLN™ cigarette smoking, indicate that exclusively smoking VLN™ cigarettes results in an approximate 97% reduction in plasma nicotine levels compared to smoking usual brand (UB) normal nicotine content (NNC) cigarettes. Findings from the applicant's submitted literature review on biomarkers of exposure (BOE) support these data, noting that smokers who primarily smoke or switch completely to smoking VLNC cigarettes (i.e., reduced nicotine content cigarettes that are identical or similar in nicotine content to VLN™ cigarettes) have reduced exposure to nicotine compared to smoking usual brand (UB) NNC cigarettes. The literature finds that exclusively smoking VLNC cigarettes across five days results in an average 94% reduction in urinary total nicotine equivalents (TNE). As such, by exclusively smoking VLNC cigarettes, consumers could reduce their exposure to nicotine by approximately 95%. As a result, I find this claim substantiated.

Regarding the claims about reduced nicotine consumption (Claims #2 and #3), both these claims are supported by evidence included in the BCP review. Given the 95% reduced nicotine content in VLN™ cigarettes, data support that menthol and non-menthol smokers who primarily smoke VLN™ cigarettes and occasionally dual use, with other tobacco or nicotine-containing products, still experience the benefit of substantially reducing their overall exposure to nicotine compared to exclusively smoking UB-NNC cigarettes. When considering the range of non-compliance across the sample of participants assigned to smoke VLNC cigarettes (i.e., the number of UB cigarettes smoked during the course of the study in addition to VLN™ cigarettes), studies in the literature report an average 59-60% reduction in nicotine exposure over 6 to 20 weeks of VLNC cigarette use. The applicant's 6-week longitudinal study supports that, as a result of substantially reducing nicotine exposure, switching to VLNC cigarettes can lead to smoking fewer overall cigarettes per day (CPD) compared to ongoing UB-NNC cigarette smoking. These findings are supported by several VLNC cigarette studies in the published literature, including a 20-week study of VLNC cigarette use among smokers, which is the longest study of VLNC cigarettes to date (Hatsukami et al., 2018). On average, smokers assigned to switch to VLNCs had half the CPD compared to those in the UB-NNC control group. The extent of cigarette reduction depends on the extent of switching to smoking VLN™ cigarettes, although smokers who occasionally smoke UB-NNC cigarettes still experience a significant reduction in CPD compared to smoking UB-NNC cigarettes exclusively. Studies support that as the duration of smoking VLNC cigarettes increases, the reduction in CPD increases. Thus, the available evidence supports Claims #2 and #3.

In sum, consistent with section 911(g)(2)(A)(i), I find that the magnitude of the overall reduction in exposure to nicotine in VLN™ is substantial, and VLN™ as actually used exposes consumers to the specified reduced level of nicotine. Also, I find that nicotine is harmful. It is addictive and is a reproductive or developmental toxicant (RDT) in FDA's established list of harmful and potentially harmful constituents.

Individual health impact among tobacco users

The totality of evidence presented suggests that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies. This determination predominantly stems from: (1) the 95% reduction in nicotine exposure with exclusive use of VLN™ cigarettes and at least about 50% reduction in nicotine exposure with dual use with NNC cigarettes; (2) the reduced abuse liability of VLN™ cigarettes and reduced nicotine dependence among users; (3) the substantial reduction in CPD among smokers who predominantly use VLN™ cigarettes (an estimated 50% reduction); and (4) the reduction in some tobacco morbidities (e.g., lung cancer) associated with at least a 50% reduction in CPD. Specifically, in addition to the substantiation of claims about nicotine, FDA found that VLN™ cigarettes had low subjective effects ratings and lower dependence scores. Consistent with this, clinical studies of smokers who do not want to quit found that, even among smokers who continue to use NNC cigarettes, CPD decreases over the course of using VLN™ cigarettes. The longest clinical study, lasting 20 weeks, found that smokers assigned to use VLNC cigarettes had 50% lower CPD compared to smokers assigned to smoke NNC cigarettes (Hatsukami et al., 2018). Published literature finds that reducing cigarette consumption can increase the likelihood that an individual will become cigarette abstinent in the future. Additionally, as discussed further in our evaluation of population health impact, published epidemiological studies assessing the relationship between smoking reduction and disease risks suggested a potential benefit for some health endpoints such as lung cancer risk in those who reduced CPD by more than 50% compared to non-reducers. While past studies have not consistently demonstrated that a reduction in CPD reduces mortality, a recent study that evaluated changes in smoking patterns over a longer period of time than previous studies found that all-cause mortality was lower among smokers who reduced their CPD compared to those who maintained their CPD, with greater reductions in CPD yielding greater benefits (Inoue-Choi et al., 2019). Therefore, I find that the scientific evidence demonstrates that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies.

Consumer understanding

In terms of consumer understanding, the applications support the findings required for authorization. Actual consumer perception testing overall supports that consumers understood the claims, including the applicant requested claims (#1-3) and the FDA identified claims (#4-10). Consumers understood that the claims refer to the nicotine content and nicotine exposure from VLN™ cigarettes themselves, rather than users' overall nicotine consumption, and that exposure to nicotine from VLN™ cigarettes is substantially lower than from other cigarettes on the market. Findings from the applicant's quantitative study suggest that the proposed LLA would enable consumers to understand the addiction risks of smoking VLN™ cigarettes. Consistent with VLN™ cigarette's very low nicotine level, participants perceived VLN™ cigarettes as substantially less addictive than other cigarettes after viewing the VLN™ cigarette pack image with the proposed modified risk claims. At the same time, participants still perceived some risk of addiction from smoking VLN™ cigarettes, placing them in a similar range as NRT. Participants also perceived health risks of using VLN™ cigarettes (other than addiction) as moderate to high, and higher than that of NRT.

However, the proposed LLA include no information on conditions of use, such as how consumers should use VLN™ cigarettes to reduce their exposure to HPHCs and potential disease risk. It was unclear whether smokers intended to use VLN™ cigarettes to cut down on their overall cigarette consumption or simply replace all or some of their current cigarette use with VLN™ cigarettes. This made it challenging

to evaluate the finding that after viewing VLN™ cigarette packs with the proposed modified risk information, participants perceived VLN™ cigarettes as presenting lower risks of tobacco-related diseases-- including lung cancer, mouth/throat cancer, heart disease, and 15 other tobacco-related diseases and health effects -- compared to other cigarettes. This was particularly challenging to evaluate because the survey questions did not include information regarding patterns or frequency of use (i.e., whether VLN™ cigarettes would be used at the same rate or be used to cut down), and the research did not assess the assumptions participants made in answering these questions. Thus, it was difficult to evaluate whether consumers believed using the products would result in lower risk because of smoking reduction and/or eventual abstinence (correct), or because lowering nicotine and smoking the same amount would lead to a risk reduction (incorrect). These findings indicate that without additional corrective or clarifying information, many U.S. consumers are at risk of misinterpreting statements about reduced nicotine content cigarettes. To address this issue, under section 911(h)(3)(B), I recommend that the order require VLN™ cigarettes' modified risk LLA to include an explicit statement about the manner in which the product must be used in order to obtain a benefit ("Helps you smoke less"). Some of the applicant's research included this statement and found it to be generally well understood by consumers. By including this statement in a way that will be noticed and read, the LLA will enable consumers to better understand the significance of the reduced nicotine claims, the relevance to their personal health (or the irrelevance, if the person does not wish to smoke less), and the reason why the manufacturer would be providing the information about nicotine to consumers. This will enable consumers to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health.

Additionally, the authorization letter for the proposed MRTPs should recommend that the applicant include the disclaimer "Nicotine is addictive. Less nicotine does NOT mean safer…" on VLN™ cigarette pack LLA, given that it was present on all of the labeling that the applicant tested in its quantitative consumer research. The letter should also require the applicant to test the disclaimer in a postmarket study. Several aspects of the disclaimer are inconsistent with expert recommendations for disclaimers, and prior research suggests that poorly designed disclaimers can confuse consumers and change their perceptions, attitudes, or decisions in a manner opposite of that intended (Green & Armstrong, 2012). In a pre-submission meeting with the applicant, FDA recommended that the applicant conduct a study comparing consumer understanding across participants who did and did not see the disclaimer, to assess the disclaimer's effects on understanding of the modified risk information. However, the applicant submitted no evidence of the disclaimer's effect on consumer understanding. Conducting a postmarket test can provide FDA with evidence about whether the disclaimer helps enable consumers to understand that VLN™ cigarettes present the same disease risks as other cigarettes if smoked in the same way, or whether it confuses people about the health risks of VLN™ cigarettes. Thus, I recommend that the order require the applicant to conduct such a study of the disclaimer as part of postmarket surveillance; this is discussed further below in Section IV(C).

Social science did not specifically evaluate consumer understanding of FDA-identified Claims #4-10, in detail. These statements appear to convey the same information as applicant-identified Claims #1-3. Specifically, these claims are limited to information about VLN™ cigarettes' nicotine content and how it compares with that of other cigarettes, although some of the claims describe the nicotine content in absolute terms (e.g., ".27 mg"), use qualitative comparisons (e.g., "substantially lower"), or include comparators (e.g., "the top 100 cigarette brands"). However, the applicant's qualitative research on consumer understanding (described in the social science review Section 4; M/A/R/C Qualitative Study) examined participants' responses to claims with alternate phrasing similar to these variations. The one

exception is Claim #9, which describes the source of VLN™ cigarettes' reduced nicotine content (i.e., "unique technology and plant breeding expertise" allows the company to grow tobacco with different nicotine levels). This statement is similar to background information about VLN™ cigarettes viewed by participants in the applicant's quantitative consumer perception research (see Sections 4 and 5 of the social science review; M/A/R/C Research Quantitative Study). The background information stated: "A new tobacco product called VLN™ (Very Low Nicotine) is currently in development… VLN™ cigarettes are made from a tobacco plant that has been altered to contain much lower levels of nicotine than the tobacco used in traditional cigarettes." Thus, although the applicant did not specifically examine consumer responses to Claims #4-10, any potential concerns are mitigated by the fact that these claims appear to convey the same information as Claims #1-3 and the information participants viewed in the applicant's quantitative consumer research.

Population Health Impact

The available scientific evidence demonstrates that the issuance of an exposure modification order for VLN™ cigarettes would be appropriate to promote the public health and 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. The longest clinical study of VLNC cigarettes, lasting 20 weeks, found that smokers assigned to use VLNC cigarettes had 50% lower CPD compared to smokers assigned to smoke NNC cigarettes (Hatsukami et al., 2018). Across clinical studies, most smokers instructed to exclusively use VLN™ cigarettes still used several NNC cigarettes per day, and still experienced CPD reductions. Published literature finds that reducing cigarette consumption can increase the likelihood that an individual will become cigarette abstinent in the future. Additionally, published epidemiological studies assessing the relationship between smoking reduction and disease risks suggested a potential benefit for some morbidities (such as lung cancer) in those who reduced CPD by more than 50% compared to non-reducers. While past studies have not consistently demonstrated that a reduction in CPD reduces mortality, a recent study evaluating changes in smoking patterns over a longer period of time found that all-cause mortality was lower among smokers who reduced their CPD compared to those who maintained their CPD, with greater reductions in CPD yielding greater benefits (Inoue-Choi et al., 2019). Therefore, I find it is reasonably likely that the scientific evidence demonstrates that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies.

After viewing product labels with the exposure reduction claims, many current smokers were interested in VLN™ cigarettes (mean intentions were above the midpoint of the scale), and smokers had significantly higher intentions to purchase the proposed MRTPAs compared to Marlboro Gold™ cigarettes. Current smokers also reported substantially higher intentions to use VLN™ cigarettes on a regular, ongoing basis compared to Marlboro Gold™. Additionally, adult never smokers and former smokers had low intentions to buy and use VLN™ cigarettes (mean intentions were near the bottom of the scale), and these intentions were similar to or slightly higher than their intentions to buy and use Marlboro Gold™. Furthermore, while the applicant's population model predicted 340,000 avoided cigarette-attributable deaths by year 2100, this model may have overestimated population benefits (e.g., due to overestimating market share). Still, overall, FDA concluded that there are likely to be some benefits of smokers switching to VLN™ cigarettes and low uptake of nonusers.

The application did not provide information about the likelihood that youth would use VLN™ cigarettes if marketed with the proposed modified risk information. However, FDA has low concern about youth

initiation and progression to regular use, because: the products have low abuse liability and youth may be less likely to develop nicotine dependence using them; young adults rate VLNCs as having lower subjective effects compared to NNC cigarettes; and a study of adolescents found that the reinforcing efficacy or appeal of all doses of VLNC cigarettes was lower compared to UB-NNC cigarettes (Cassidy et al., 2019). Still, as discussed below in Section IV(C), given that youth are at increased risk for tobacco initiation and the potential effect of modified risk information on youth use, it is critical that any marketing plans be designed to prioritize preventing youth exposure. Studies suggest that perceptions of risk predict tobacco product use among youth (Song et al., 2009) (Strong et al., 2019). FDA's PMTA marketing authorization order for the products includes postmarket requirements to help limit youth exposure to product marketing. This includes: informing FDA of all marketing plans, restricting youth exposure to the products' LLA, and requiring the applicant to measure actual delivery of advertising to youth. In addition, postmarket surveillance studies should be conducted to monitor youth awareness and use of the proposed MRTPs to ensure that their marketing will not have the unintended consequence of leading to increased use of these products among youth.

Section 911(g)(2)(C)(i) of the FD&C Act provides that an MRTP exposure modification order shall be limited for a term of not more than 5 years. I recommend authorization for a period of 5 years, given the low abuse liability of this product. Although this review has found that an exposure modification order for the products would be appropriate to promote the public health and is expected to benefit the health of the population as a whole, that determination may change over time as a function of how the products are actually used by consumers. Therefore, monitoring use of the proposed MRTPs in terms of uptake, dual use, and complete switching should be required, including the potential for initiation among youth. As described below, postmarket surveillance and studies must include an assessment of MRTP users' behavior and understanding over time. A 5-year period is a reasonable amount of time to assess whether there is appropriate consumer understanding and to generate preliminary data on behavior in postmarket surveillance and studies to assess whether the standard continues to be met and whether the order should be renewed. In addition, this order should require a study on the independent effects of the disclaimer, since it is unclear whether the disclaimer benefits or reduces consumers' ability to understand the risks of using the proposed MRTPs.

B. Environmental Impact

A finding of no significant impact (FONSI) was signed by Luis Valerio Jr. Ph.D. on December 15, 2021. The FONSI was supported by an environmental assessment prepared by FDA on December 15, 2021.

C. Postmarket Surveillance and Studies (PMSS)

I recommend that the order include the following language in the marketing authorization:

Under section 911(g)(2)(C)(ii) of the FD&C Act, an order under 911(g)(2) is conditioned on the applicant's agreement to conduct postmarket surveillance and studies in order to "determine the impact of the order on consumer perception, behavior, and health, and to enable the [FDA] to review the accuracy of the determinations upon which the order was based in accordance with a protocol approved by the [FDA]."

1. PMSS Content

a. MRTP Use Behavior and Consumer Understanding and Perception

After receiving authorization, the determination of whether the tobacco products, which are the subject of this order, continue to satisfy the requirements of section 911(g)(2)(A) and (B), is driven, in part, by use behavior.

Your proposed postmarketing surveillance and studies (PMSS) include a 6-month cross sectional study (n=1,000) to assess product knowledge, use, and attitudes among people who started smoking VLN™ cigarettes within the past 6 months (Section X "Postmarket Surveillance Program," pp. 5-6). Primary objectives of the study would be to assess VLN™ product knowledge, use patterns, and demographic characteristics of VLN™ smokers (age, gender, ethnicity, three-digit zip code). Secondary objectives would be to assess the use of other tobacco products at the time of initiation of VLN™ cigarettes, describe how users learned about VLN™ cigarettes, and describe personal factors motivating initiation of VLN™ cigarette use. You also propose to recruit a subset of the cross-sectional study participants into a longitudinal study that would evaluate reductions in cigarette use among VLN™ smokers prospectively over a 12-month period. We agree with the constructs you propose to assess in your 6-month cross-sectional study (e.g., knowledge of VLN™'s product features – including understanding of the health risks associated with various patterns of use – as well as demographic characteristics and current, previous, and subsequent use patterns with VLN™ and other cigarettes). In your longitudinal study, monitoring use of the products that are the subject of this order in terms of uptake, dual use, and complete switching is required. In particular, your PMSS must assess the extent to which new MRTP users were never, former, or current smokers, or other tobacco product users before initiating the MRTPs and the extent to which new users of the MRTPs become exclusive VLN™ cigarette users, dual users with combusted cigarettes or other tobacco products, or transition to normal nicotine content (NNC) cigarette smoking over time. These studies must be designed to observe behavior over a sufficient period of time to examine, for instance, the extent to which dual use of VLN™ cigarettes and combusted cigarettes is a transitional versus stable pattern of use.

Your studies must also include an assessment of consumers' understanding of the modified risk claims and perceptions of the products. In particular, PMSS must assess the extent to which users of these products understand that VLN™ cigarettes are just as toxic as other cigarettes when used in the same way (i.e., with the same frequency and for the same duration). Additionally, you must assess the extent to which VLN™ cigarette users understand that to get long-term benefits, they have to use VLN™ cigarettes to substantially reduce the amount of cigarettes that they smoke. Thus, you must assess whether current smokers who take up VLN™ understand that they should cut down on their overall cigarette smoking and that replacing their other cigarettes with VLN™ without substantially cutting down is not sufficient to yield long-term benefits.

Your studies must have clear research objectives, including assessing whether the MRTPs are leading to changes in product use behaviors that are expected to benefit population health. Your protocol must include a statistical analysis plan describing, among other things, how you plan to conduct inferential statistical analyses to address these objectives.

Your PMSS must also include a postmarket study testing the effects of the disclaimer[11] ("Nicotine is addictive. Less nicotine does NOT mean safer. All cigarettes can cause disease and death.") on consumer understanding of VLN™ cigarettes' health risks and conditions of use. The disclaimer has several features that are inconsistent with expert recommendations for designing disclaimers, and poorly designed disclaimers have the potential to confuse consumers and change their perceptions, attitudes, or decisions in a manner opposite of that intended (Green & Armstrong, 2012). Conducting a postmarket study to test the disclaimer can provide FDA with evidence about whether the disclaimer helps enable consumers to understand that VLN™ cigarettes present the same disease risks as other cigarettes if smoked in the same way, or if it worsens existing misperceptions about the health risks of cigarettes containing reduced nicotine levels. If FDA determines that the disclaimer causes such misperceptions, then FDA will require that you remove the disclaimer from the modified risk labels, labeling and advertising and any advertising where it is included.

FDA also recommends that, if you seek to use any modified risk ads that are potentially youth-appealing, then you should conduct consumer testing of the ads to determine whether they would increase the likelihood of use among nonsmokers, particularly minors (under age 21). (b) (4) we suggest that if you seek to use ads that are potentially youth appealing, then you first study them to determine the effect on initiation by non-users, particularly youth; imagery and themes known to resonate with youth include aspirational content depicting tobacco use as "cool," attractive, rebellious, or risky, or as a means to make one more popular, desirable, or independent (U.S. Department of Health and Human Services, 2012).

In addition, FDA has determined that assessing the impact of your MRTP orders on uptake of the products requires surveillance of MRTP sales and distribution, which provide information to assess tobacco consumption at the population level. Your PMSS protocols must describe procedures for monitoring and reporting MRTP sales and distribution in the U.S. by product, major metropolitan areas, and channels where the products are sold (e.g., convenience stores, food and drug stores, internet and digital retailers, tobacco specialty shops). Your annual PMSS report must include:

- U.S. sales and distribution of the tobacco products by quarter since the date of issuance of your modified risk granted orders (for the initial reporting period) or the previous reporting period (for all reports that follow), including, for each MRTPA STN, total U.S. sales and distribution reported in dollars and units, and broken down by major metropolitan areas, and channels where the products were distributed and sold during the reporting period (e.g., convenience stores, food and drug stores, internet and digital retailers, tobacco specialty shops).

- A brief synthesis and summary of the sales and distribution data for the initial reporting period or the previous reporting period (for all reports that follow), including annual and quarterly

[11] In your MRTPAs, you refer to the statement, "Nicotine is addictive. Less nicotine does NOT mean safer. All cigarettes can cause disease and death." variously as a "disclaimer" (Section V "Labels, Labeling, and Advertising," p. 3; Section VII "Summary of All Research Findings," p. 72) and "voluntary warning" (Section V "VLN™ Cigarettes: Labels, Labeling, and Advertising," pp. 2, 8-9). In this order, the word "disclaimer" refers to your use of this term and does not reflect FDA's independent conclusion regarding characterization of the information.

growth rate (percent change) in total U.S. sales and distribution of the tobacco products for each MRTPA STN, post-MRTP authorization.

b. MRTP Use and Health Risk – Serious and Unexpected Adverse Experiences

In order for FDA to determine whether the tobacco products that are the subject of this order continue to be appropriate to promote the public health and continue to be expected to benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products (section 911(g)(2)(A-B)), your PMSS must include ongoing surveillance of all adverse experiences. These experiences may become known to you through any source, including a customer complaint, request, or suggestion made as a result of an adverse experience; or tobacco product defect, or failure, reported to you, or identified in the literature or media. Your PMSS protocols must include procedures for monitoring and analyzing adverse experiences and your annual PMSS report must include:

- A summary of reported serious and reported unexpected adverse experiences for the tobacco products, which includes a listing of all serious and unexpected adverse experiences during the reporting period and a cumulative list including all serious and unexpected adverse experiences previously reported. The summary must be accompanied by an analysis of the reports and a statement of any changes to risk information related to the products including nature, frequency, and potential aggravating factors.

In addition, the PMTA order for your tobacco products, issued on December 17, 2019, requires you to report to the FDA all adverse experiences that are serious, whether expected or unexpected, and your analysis of the association between the adverse experience and the tobacco product within 15 calendar days after the report is received by you. These experiences may become known to you through any source, including a customer complaint, request, or suggestion made as a result of an adverse experience, tobacco product defect, or failure, reported to you, or identified in the literature or media. We request that when submitting such reports, you reference both your PMTAs and your MRTPAs for these products. Your information should be submitted with a cover letter that includes the following text in the subject line: **SERIOUS ADVERSE EXPERIENCE REPORT FOR STNs PM0000491-PM0000492 and MR0000159-MR0000160**.

For purposes of this reporting, *serious adverse experience* means an adverse experience that results in any of the following outcomes:

- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or

- Any other adverse experience that, based upon appropriate medical judgment, may jeopardize the health of a person, and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

For purposes of this reporting, *unexpected adverse experience* means an adverse experience occurring in one or more persons in which the nature, severity, or frequency of the experience is not consistent with:

- The known or foreseeable risks associated with the use or exposure to the tobacco product as described in the PMTA (including the results of human subject investigations) and other relevant sources of information, such as postmarket reports and studies;

- The expected natural progression of any underlying disease, disorder, or condition of the person(s) experiencing the adverse experience and the person's predisposing risk factor profile for the adverse experience; or

- The results of nonclinical laboratory studies.

c. Surveillance of New Research Study Findings on the MRTPs and Consumer Perception, Behavior, or Health

In order for FDA to determine whether the tobacco products that are the subject of this order continue to be appropriate to promote the public health and continue to be expected to benefit the health of the population as a whole, your PMSS must include surveillance of new research study information about the MRTPs and consumer perceptions, behavior, or health. In particular, your PMSS protocol must include procedures for monitoring and assessing previously unreported (new) findings both in published or unpublished studies conducted by you or on your behalf and in published or otherwise available studies regarding the MRTPs and consumer perceptions, behavior, or health. Your annual PMSS report must include:

- (1) A summary of significant findings about the tobacco products from research studies conducted by you or on your behalf, whether or not such studies were specifically required under this order. (2) A summary of significant findings in publications not previously reported and full copies of the articles. These must include any new scientific data (published or otherwise) on the MRTPs and consumer perception, behavior, or health.

d. Modeling the Impact of the MRTP on Population Health

In order for FDA to determine whether the tobacco products that are the subject of this order continue to be appropriate to promote the public health and continue to be expected to benefit the health of the population as a whole, your PMSS must include computational modeling of the impact of the MRTPs on population health. Such modeling must incorporate data and information collected through PMSS, including the percentage of former smokers who start using VLN™ cigarettes; the percentage of current smokers who start using VLN™ cigarettes and become dual users; the percentage of current smokers who switch completely to VLN™ cigarettes; the percentage of youth and young adults under the federal minimum age of sale of tobacco products who start using VLN™ cigarettes; and the percentage of individuals who start using VLN™ cigarettes and then initiate or re-initiate NNC combusted cigarettes.

Postmarket modeling must also incorporate the latest information on acute and long-term health effects of using the proposed MRTPs relative to NNC combusted cigarette smoking in order to assess the short and long-term population health impacts of the marketing. Your annual PMSS report must include:

- A description of the methodological approach used in the model;
- A copy of the model or its underlying code, such that FDA can independently run and verify the model inputs and outputs;
- A description of all model inputs, including the justification for input values and how they were derived from postmarket data and information; and
- A summary of the modeling results and their implications for assessing whether the MRTPs continue to be appropriate to promote the public health and continue to be expected to benefit the health of the population as a whole.

2. Submitting PMSS Protocols and Reports

As required under section 911(g)(2)(C)(ii) of the FD&C Act, your modified risk order is conditioned on your agreement to conduct PMSS under an approved protocol, and to submit the results for FDA to determine the impact of the order and review the accuracy of determinations on which the order is based. Within 30 days of receiving this notice, you must submit your agreement to conduct PMSS and complete protocols for your PMSS. Label your submission clearly as a "PMSS Protocol" and reference your MRTPA Submission Tracking Numbers (STNs). If you have more than one protocol, each protocol should be a separate submission. If applicable, each protocol should include the name(s) of the principal investigator(s) and materials that demonstrate the relevant professional credentials and training that qualify them to lead the study. Within 60 days of receipt of the protocol(s), FDA intends to review the protocol(s) and evaluate if the principal investigator proposed to be used in the surveillance has sufficient qualifications and experience to conduct the surveillance and if the protocol(s) will result in collection of data or other information that has the potential to enable FDA to accurately determine the impact of the order on consumer perception, behavior and health and to review the accuracy of the determinations upon which the order was based, pursuant to section 911(g)(2)(C)(ii) of the FD&C Act. FDA will notify you of, and provide opportunities to address, any deficiency in the submission. If the PMSS protocol is amended subsequent to FDA approval, FDA must receive the amended protocol promptly. For protocol amendments that are administrative in nature (e.g., corrections in punctuation or titles), the amended protocol must be received by FDA within 30 days of the update. For protocol amendments that seek to modify the study design (including endpoints, sites, questionnaires, methodology, etc.) or other scientific parameters, you may not initiate the change until you receive FDA approval.

As part of the requirement to conduct PMSS, you must initiate and conduct your PMSS per the timeframes established in your protocols and approved by FDA. Note that for PMSS that involve human subjects, the anticipated start date for each study must account for the time required for securing IRB approval, as needed. In addition to specifying the start date, your protocols must contain timelines for completion of major study milestones including, as applicable, the start and completion of participant recruitment, initiation of data collection (per wave, if applicable), completion of data collection, analysis,

and report writing. If you deviate from these timelines, we request that you report the deviation within 30 days to FDA.

Section 911(g)(2)(C)(iii) requires that the results of the PMSS be submitted on an annual basis. These reports must be identified as “PMSS Report” and the MRTPA STNs should be referenced for each report. The PMSS Report must indicate the beginning and ending date of the period covered by the report and must include accomplishments since the last reporting period. For quantitative updates on studies in progress (e.g., participant accrual), reports should describe both interim (since the last reporting period) as well as cumulative (since study initiation) accomplishments. The PMSS Report describing studies in progress must describe the status of PMSS, including, as applicable, the status of recruitment, data collection, and analysis; a summary of the study milestones achieved and any deviations from the approved timelines in the protocol; a summary of protocol amendments; and a summary of any preliminary analyses conducted. Once a study is completed, the PMSS Report should include the complete final study report.

References

Babb, S., Malarcher, A., Schauer, G., Asman, K., Jamal, A. (2017). Quitting smoking among adults - United States, 2000-2015. *MMWR, 65*(52), 1457-1464. doi:10.15585/mmwr.mm6552a1

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*(4), 678-686. doi: 10.1093/her/cyp069

Bjartveit, K. & Tverdal, A. (2005). Health consequences of smoking 1-4 cigarettes per day. *Tobacco Control, 14*(5), 315-320.

Bolliger, C. T. (2000). Practical experiences in smoking reduction and cessation. *Addiction, 95*(Suppl 1), S19-S24.

Bolliger, C. T., Zellweger, J. P., Danielsson, T., van Biljon, X., Robidou, A., Westin, A., Perruchoud, A. P., Säwe, U. (2002). Influence of long-term smoking reduction on health risk markers and quality of life. *Nicotine Tobacco Research, 4*(4), 433-439.

Borrelli, B. & Novak, S. P. (2007). Nurses' knowledge about the risk of light cigarettes and other tobacco "harm reduction" strategies. *Nicotine Tobacco Research, 9*(6), 653-661. doi: 10.1080/14622200701365202

Brose, L. S., Brown, J., Hitchman, S. C., McNeill, A. (2015). Perceived relative harm of electronic cigarettes over time and impact on subsequent use. A survey with 1-year and 2-year follow-ups. *Drug and Alcohol Dependence. 157*, 106-111. doi: 10.1016/j.drugalcdep.2015.10.014

Burchfiel, C. M., Marcus, E. B., Curb, J. D., Maclean, C. S., Vollmer, W. M., Johnson, C. R., . . . Buist, A. S. (1995). Effects of smoking and smoking cessation on longitudinal decline in pulmonary function. *American Journal of Respiratory Critical Care Medicine, 151*(6), 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*(6), 712-714. doi: 10.1136/tobaccocontrol-2017-054124

Byron, M. J., Hall, M. G., King, J. L., Ribisl, K. M., Brewer, N. T. (2019). Reducing nicotine without misleading the public: Descriptions of cigarette nicotine level and accuracy of perceptions about nicotine content, addictiveness, and risk. *Nicotine Tobacco Research*, *21*(Suppl 1), S101-S107. doi: 10.1093/ntr/ntz161

Cassidy, R. N., Colby, S. M., Tidey, J. W., Jackson, K. M., Cioe, P. A., Krishnan-Sarin, S., & Hatsukami, D. (2018). Adolescent smokers' response to reducing the nicotine content of cigarettes: Acute effects on withdrawal symptoms and subjective evaluations. *Drug and Alcohol Dependence, 188,* 153-160. doi:10.1016/j.drugalcdep.2018.04.006

Cassidy, R. N., Tidey, J. W., Cao, Q., Colby, S. M., McClernon, F. J., Koopmeiners, J. S., . . . Donny, E. C. (2019). Age moderates smokers' subjective response to very low nicotine content cigarettes: evidence from a randomized controlled trial. *Nicotine & Tobacco Research, 21*(7), 961-969. doi:10.1093/ntr/nty079

Cheah, N. P., Borst, S., Hendrickx L., Cremers, H., Jasen, E., Opperhuizen, A., Talhout, R. (2018). Effect of Adding Sugar to Burley Tobacco on the Emission of Aldehydes in Mainstream Tobacco Smoke. *Tobacco Regulatory Science, 4*(2), 61-72

Chen, M., Xu, Z., Chen, G., Wang, H., Yin, C., Zhou, Z., et al. (2014). The influence of exogenous fiber on the generation of carbonyl compounds in reconstituted tobacco sheet. *Journal of Analytical and Applied Pyrolysis, 105,* 227-233.

Counts, M. E., Morton, M. J., Laffoon, S. W., Cox, R. H., Lipowicz, P. J. (2005). Smoke composition and predicting relationships for international commercial cigarettes smoked with three machine-smoking conditions. *Regulatory Toxicology and Pharmacology: RTP, 41*(3), 185-227.

Denlinger-Apte, R.L., Kotlyar, M., Koopmeiners, J.S., Tidey, J.W., Luo, X., Benowitz, N.L, et al. (2019). Effects of Very Low Nicotine Content Cigarettes on Smoking Behavior and Biomarkers of Exposure in Menthol and Non-menthol Smokers. *Nicotine and Tobacco Research, 21(Supplement 1),* S63-S72.

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*(10), 1149-1154. doi: 10.1093/ntr/ntw320.

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*(6), 536-539. doi:10.1136/tobaccocontrol-2014-051797

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*(14), 1340-1349. doi:10.1056/NEJMsa1502403

Donny, E. C., & Jones, M. (2009). Prolonged exposure to denicotinized cigarettes with or without transdermal nicotine. *Drug and Alcohol Dependence, 104*(1-2), 23-33. doi:10.1016/j.drugalcdep.2009.01.021

Edwards, S.H., Rossiter, L.M., Taylor, K.M., Holman, M.R., Zhang, L., Ding, Y.S., Watson, C.H. (2017). Tobacco-Specific Nitrosamines in the Tobacco and Mainstream Smoke of U.S. Commercial Cigarettes. *Chemical Research in Toxicology, 20*(30), 540-551.

Eliasson, B., Hjalmarson, A., Kruse, E., Landfeldt, B., Westin, A. (2001). Effect of smoking reduction and cessation on cardiovascular risk factors. *Nicotine Tobacco Research, 3*(3), 249-255.

Elton-Marshall, T., Driezen, P., Fong, G. T., Cummings, K. M., Persoskie, A., Wackowski, O., … Hyland, A. (2020). Adult perceptions of the relative harm of tobacco products and subsequent tobacco product use: Longitudinal findings from Waves 1 and 2 of the Population Assessment of Tobacco and Health (PATH) Study. *Addictive Behaviors, 106*, 106337. doi: 10.1016/j.addbeh.2020.106337

Foulds, J., Hobkirk, A., Wasserman, E., Richie, J., Veldheer, S., Krebs, N. M., Reinhart, L., 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., Lam, T.H., Hansel, T.T., Leon, M. E., Gray, N., Dresler, C., Burns, D. M., et al. (2008). COPD-related morbidity and mortality after smoking cessation: status of the evidence. *European Respiratory Journal, 32,* 844-83.

Godtfredsen, N. S., Osler, M., Vestbo, J., Andersen, I., Prescott, E. (2003). Smoking reduction, smoking cessation, and incidence of fatal and non-fatal myocardial infarction in Denmark 1976-1998: a pooled cohort study. *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*(12), 1505-1510

Godtfredsen, N. S., Vestbo, J., Osler, M., Prescott, E. (2002). Risk of hospital admission for COPD following smoking cessation and reduction: a Danish population study. *Thorax. 57*(11), 967-972.

Green, K. C. & Armstrong, J. S. (2012). Evidence on the effects of mandatory disclaimers in advertising. *Journal of Public Policy and Marketing. 31*(2), 293-304. doi: 10.1509/jppm.12.053

Hatsukami, D. K., Heishman, S. J., Vogel, R. I., Denlinger, R. L., Roper-Batker, A. N., Mackowick, K. M., . . . Donny, E. (2013). Dose-response effects of spectrum research cigarettes. *Nicotine & Tobacco Research, 15*(6), 1113-1121. doi:10.1093/ntr/nts247

Hatsukami, D. K., Kotlyar, M., Allen, S., Jansen, J. M. S., Li, S., Le, C., Murphy, S. (2005). Effects of cigarette reduction on cardiovascular risk factors and subjective measures. *Chest, 128*(4), 2528-2537.

Hatsukami, D. K., Kotlyar, M., Hertsgaard, 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*(2), 343-355. doi:10.1111/j.1360-0443.2009.02780.x

Hatsukami, D. K., Luo, X., Dick, L., Kangkum, M., Allen, S. S. Murphy, S. E., Hecht, S. S., Shields, P. G., 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*(9), 880-891. doi:10.1001/jama.2018.11473

Hatsukami, D. K., Luo, X., Heskin, A. K., Tang, M. K., Carmella, S. G., Jensen, J., Robinson, J. D., Vandrey, R., Drobes, D. J., Strasser, A. A., al'Absi, M., Leischow, S., Cinciripini, P. M., Koopmeiners, J., Ikuemonisan, J., Benowitz, N. L., Donny, E. C., and Hecht, S. S. (2019) Effects of immediate versus gradual nicotine reduction in cigarettes on biomarkers of biological effects. *Addiction, 114*, 1824– 1833. https://doi.org/10.1111/add.14695.

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 Therapeutics, 42*(2):83-92.

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. doi:10.1080/14622200600789726

Inoue-Choi, M., Hartge, P., Park, Y., Abnet, C. C., Freedman, N. D. (2019). Association Between Reductions of Number of Cigarettes Smoked per Day and Mortality Among Older Adults in the United States. *American Journal of Epidemiology, 188*(2), 363-371.

Institute of Medicine. (2010). *Committee on Examination of Front-of-Package Nutrition Rating Systems and Symbols: Phase I Report.* Washington, DC: National Academies Press. Retrieved from: https://www.ncbi.nlm.nih.gov/books/NBK209851/.

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.

Kamens, H. M., Silva, C. P., Nye, R. T., Miller, C. N., Singh, N., Sipko, J., . . . Foulds, J. (2019). Pharmacokinetic profile of Spectrum reduced nicotine cigarettes. *Nicotine & Tobacco Research, 22* (2), 273-279. doi:10.1093/ntr/ntz045

Kozlowski, L. T. & O'Connor, R. J. (2002). Cigarette filter ventilation is a defective design because of misleading taste, bigger puffs, and blocked vents. *Tobacco Control, 11*, i40-i50.

Lee, P. N. (2013). The effect of reducing the number of cigarettes smoked on risk of lung cancer, COPD, cardiovascular disease and FEV(1)--a review. *Regulatory Toxicology Pharmacology, 67*(3), 372-381.

Leistikow, B. N., Martin, D. C., Milano, C. E. (2000). Fire injuries, disasters, and costs from cigarettes and cigarette lights: a global overview. *Preventive Medicine, 31*(2), 91-99.

McRobbie, H. Przulj, D., Myers Smith, K., Cornwall, D. (2016). Complementing the standard multicomponent treatment for smokers with denicotinized cigarettes: A randomized trial. *Nicotine Tobacco Research, 18*(5), 1134-1141. doi: 10.1093/ntr/ntv122

Messer, K., Trinidad, D. R., Al-Delaimy, W. K., Pierce, J. P. (2008). Smoking cessation rates in the United States: A comparison of young adult and older smokers. *American Journal of Public Health, 98*(2), 317-322.

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*(6), 1166-1175. doi: 10.1111/j.1360-0443.2011.03402.x

Naik, P., Sajja, R. K., Prasad, S., Cucullo, L. (2015). Effect of full flavor and denicotinized cigarettes exposure on the brain microvascular endothelium: a microarray-based gene expression study using a human immortalized BBB endothelial cell line. *BMC Neuroscience, 16*, 38.

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. doi:10.1111/add.13519

Novotny, T. E., Hardin, S. N., Hovda, L. R., Novotny, D. J., McLean, M. K., Safdar, K. (2011). Tobacco and cigarette butt consumption in humans and animals. *Tobacco Control, 20*(Suppl 1):i17-i20.

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. doi: 10.1016/j.ypmed.2016.12.048

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*(4), 402-410.

Pacek, L. R., Sweitzer, M. M., McClernon, J. (2016). Non-cigarette tobacco and poly-tobacco use among persons living with HIV drawn from a nationally representative sample. *Drug and Alcohol Dependence, 162,* 251-255.

Pauwels, C. G. G. M., Klerx, W. N. M., Pennings, J. L. A., Boots, A. W., van Schooten, F. S., Opperhuizen, A., Talhout, R. (2018). Cigarette Filter Ventilation and Smoking Protocol Influence Aldehyde Smoke Yields. *Chemical Research in Toxicology, 31*(6), 462-471.

Persoskie, A. & Nelson, W. L. (2013). Just blowing smoke? Social desirability and reporting of intentions to quit smoking. *Nicotine Tobacco Research, 15*(12), 2088-2093. doi:10.1093/ntr/ntt101

Poland, B. & Teischinger, F. (2017). Population Modeling of Modified Risk Tobacco Products Accounting for Smoking Reduction and Gradual Transitions of Relative Risk. *Nicotine Tobacco Research, 19*(11), 1277-1283.

Rigotti, N. (2020). Benefits and Risks of Smoking Cessation. In J. K. Stoller, M. D. Aronson (Eds.), UpToDate. Retrieved June 12, 202 from https://www.uptodate.com/contents/benefits-and-consequences-of-smoking-cessation.

Shadel, W. G., Lerman, C., Cappella, J., Strasser, A. A., Pinto, A., Hornik, R. (2006). Evaluating smokers' reactions to advertising for new lower nicotine Quest cigarettes. *Psychology of Addictive Behaviors, 20*(1), 80-84. doi: 10.1037/0893-164X.20.1.80

Song A.V., Morrell H.E.R., Cornell J.L., et al. (2009). Perceptions of smoking-related risks and benefits as predictors of adolescent smoking initiation. *American Journal of Public Health,* 99:487-492.

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(10), 889-894.

Strasser, A. A., Tang, K. Z., Tuller, M. D., Cappella, J. N. (2008). PREP advertisement features affect smokers' beliefs regarding potential harm. *Tobacco Control, 17*(Suppl 1), i32-i38. doi: 10.1136/tc.2007.022426

Strong D.R., Leas E., Elton-Marshall T., Wackowski O.A., et al. (2019). Harm perceptions and tobacco use initiation among youth in Wave 1 and 2 of the Population Assessment of Tobacco and Health (PATH) Study. *Preventive Medicine*, 123:185-191.

Sung, H. Y., Wang, Y., Yao, T., Lightwood, J., Max, W. (2016). Polytobacco use of cigarettes, cigars, chewing tobacco, and snuff among US adults. *Nicotine Tobacco Research, 18*(5), 817-826.

Talhout, R., Opperhuizen, A., van Amsterdam, J. G. C. (2007). Role of acetaldehyde in tobacco smoke addiction. *European Neuropsychopharmacology, 17(10), 627-636.*

Thun, M. J., Carter, B. D., Feskanich, D., Freedman, N. D., Prentice, R., Lopez, A. D., Hartge, P., Gaptur, S. M. (2013). 50-year trends in smoking-related mortality in the United States. *New England Journal of Medicine, 368*(4), 351-364.

Tidey, J. W., Denlinger, R., Hatsukami, D., Donny, E. (2017). Environmental smoke exposure among daily smokers with low vs. high educational attainment. *Drug and Alcohol Dependence, 100*(171).

Tverdal, A. & Bjartveit, K. (2006). Health consequences of reduced daily cigarette consumption. *Tobacco Control, 15*(6), 472-480.

U.S. Department of Health and Human Services. (2004). *The Health Consequences of Smoking: A Report of the Surgeon General.* U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. Atlanta, GA.

U.S. Department of Health and Human Services. (2012). *Preventing Tobacco Use among Youth and Young Adults: A Report of the Surgeon General.* U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, Atlanta, GA. Retrieved from: https://www.surgeongeneral.gov/library/reports/preventing-youth-tobacco-use/full-report.pdf

U.S. Department of Health and Human Services. (2014). *The Health Consequences of Smoking--50 Years of Progress: A Report of the Surgeon General*. U.S. Department of Health and Human Services. Retrieved from Rockville, MD.

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*(10), 1857-1867. doi:10.1111/j.1360-0443.2012.03906.x